University of Alberta

Clinical and Population-Based Applications of Generic Health-Related Quality of Life Measures in Type 2 Diabetes

by

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Abstract

Health-related quality of life (HRQL) is an important outcome in chronic diseases such as diabetes, particularly from a patient perspective. In order for HRQL data to be useful in informing policy or clinical decisions, it is essential that these data are measured using an instrument that is valid in the particular disease under study. The objectives of this program of research were to (1) generate initial evidence of the construct validity of three generic measures of HRQL (specifically, the RAND-12 and Health Utilities Index Mark 2 and Mark 3) in type 2 diabetes and (2) assess the importance of a broad range of determinants of health in type 2 diabetes at the population level. Two sources of data were used in the analyses: a clinical trial sample from the Diabetes Outreach Van Enhancement (DOVE) Study and data from a representative population-based sample of community dwelling Canadians. The RAND-12 performed reasonably well in discriminating between individuals expected to differ in their level of HRQL according to duration of diabetes, insulin use and days off work for diabetes. The HUI2 and HUI3 overall scores discriminated well according to duration of diabetes, treatment regimen, days off work, emergency room visits, and comorbidities, with larger differences detected by the HUI3. This suggested that the HUI3 may be preferred in type 2 diabetes over the HUI2. Evidence of the ability of the HUI3 to discriminate according to duration of diabetes and treatment regimen was generated from both data sources, which increased our confidence in its performance in type 2 diabetes. As well, for the HUI3, the association between its overall scores and healthcare resource utilization provided further evidence of construct validity. In summary, evidence was generated to support the use of all three generic HRQL measures in type 2 diabetes. The determinants of health analysis

demonstrated that disease-related factors, social determinants of health, and health-related behaviours were all associated with clinically important HRQL deficits in type 2 diabetes. Many determinants that were associated with clinically important HRQL deficits (i.e. sense of belonging, life stress and food insecurity) extended beyond a medical focus on disease.

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Chapter 1 - Introduction

1.1.0 Overview

Approximately 5.2% of Canadians have diabetes, 90% of whom have type 2 diabetes.(1) This chronic condition is associated with significant health-related quality of life (HRQL) deficits.(2-7) It appears that complications associated with the disease and its treatment contribute to the overall disease burden in type 2 diabetes.(2;8-13) Cardiovascular disease, stroke and peripheral vascular disease are examples of comorbidities that can result in significant morbidity, mortality and impairment.(2;8-15) The impact of key social determinants of health on health HRQL in type 2 diabetes, however, cannot be ignored. Income, education, social support, and stress are examples of important determinants of health in the Canadian population that can affect HRQL in diabetes.(16-19) HRQL is an important patient-reported outcome in diabetes because clinical parameters, such as glycosylated hemoglobin (A1c), often fail to capture the overall impact of the disease.(20;21) A combination of patient-reported and clinical outcomes would, therefore, give a more complete understanding of the disease and its impact.

1.2.0 Health Related Quality of Life Measurement

While it is apparent that assessing HRQL in type 2 diabetes can provide useful information for many purposes (i.e. for clinical applications, health policy and resource allocation decision making and for research purposes), the most appropriate manner in which to assess HRQL in type 2 diabetes has been debated.(22) HRQL measures can be categorized as specific or generic measures. Specific HRQL measures bring into focus the impact on health and functioning arising directly from a condition or treatment and are intended to provide greater detail concerning outcomes associated with a condition.(23) To illustrate, the Diabetes Health Profile contains three dimensions: psychosocial distress, barriers to activities and disinhibiting eating, with items relating specifically to diabetes.(24) In contrast, generic HRQL measures provide information on general functioning and well-being. For example, the RAND-12 simply assesses physical and mental health without making reference to any particular disease. Despite concerns of decreased sensitivity, generic measures of HRQL have an advantage over disease specific measures in that they permit comparisons of the impact of various diseases on multiple dimensions of HRQL, which may provide useful data for policy and resource allocation decisions.(25) Much of the HRQL research in diabetes has focused on the development and application of diabetes-specific instruments.(26;27)

Generic measures of HRQL are appropriate and desirable for particular applications in diabetes. For example, diabetes specific measures may not capture the additional HRQL deficits associated with comorbidities,(9;11;28) which make an important contribution to the disease burden in type 2 diabetes. Thus, the actual choice of HRQL measure should depend on a number of factors such as the purpose of the measurement, the attributes of health that are relevant to the target population, in addition to the evidence of construct validity (defined as the degree to which an instrument measures the property or concept that it is intended to measure)(29) of the measure in the target population.

Generic measures can be classified into health status profiles and preference-based index measures.(23) Profile measures provide an array of scores representing various dimensions of health status or HRQL. Examples of profile measures include the Short-Form 36 (SF-36) and the Nottingham Health Profile. Such measures provide multiple outcome scores that may be useful to clinicians and researchers for monitoring or measuring differential effects of a condition or treatment.

1.3.0 RAND-12

As previously described, the RAND-12 is a generic profile measure of HRQL that assesses health status on two dimensions: physical and mental health. It has not been used to study HRQL in diabetes and past research using the 36-item version of the instrument (the RAND-36) in diabetes is limited. Many studies have applied the SF-36 in diabetes, but differences in the scoring algorithms(30), number of items and domains captured by the instruments attenuates the generalization of SF-36 results to the RAND-12. The RAND-12 has reduced respondent burden compared to the RAND-36 and SF-36. Further, it may be easier to use the results obtained from two summary scales scores, as opposed to eight dimensions on the SF-36. There is, however, potential for loss of information with the 12-item measure relative to the RAND-36. The RAND-12 also has potential advantages over the SF-12 in the application of item-response theory in the scoring algorithms, as well as allowing correlation been the physical and mental dimensions (oblique factors) of HRQL, while the SF-12 does not allow the dimensions to correlate (orthogonal factors).(31) The RAND-12 would seem to be a suitable measure in type 2 diabetes as diabetes would likely affect both physical and mental health. Thus the RAND-12 warrants further investigation.

1.4.0 Utility Measures and the Health Utilities Index Mark 3

Preference-based index measures are based upon decision theory and economics and reflect preferences for alternative health outcomes.(23) An index produces a single overall score that reflects the value associated with a health state. Scores are often referred to as 'utility scores' or 'utilities'. Index scores are presented on a scale of 0 to 1, conventionally anchored as 'dead' and 'full health', respectively. Preference-based measures can be direct or indirect. Examples of direct measures include the standard gamble (SG) and the time trade-off (TTO).

Indirect preference-based measures are often referred to as multi-attribute measures. A multi-attribute utility measure defines health states with a set of attributes using a classification system. For example, the Health Utilities Index Mark 3 (HUI3) defines health on eight attributes: vision, hearing speech, ambulation, dexterity, emotion, cognition and pain. The level of functioning on each attribute is determined using a questionnaire. A multi-attribute utility function is then used to assign a valuation to a health state defined by the level of functioning on each attribute. The valuation is based upon community (i.e. societal) preferences for the health states described in the classification system. In addition to the overall index score, multi-attribute utility measures also provide information on specific attributes of health. Depending on the attributes measured, these measures may be able to capture condition-specific information on health status if the dimensions captured in the measure are those likely to be affected by the disease.(23)

The Health Utilities Indices (HUI) are a family of preference-based measure that may be particularly useful for assessing HRQL in type 2 diabetes since the attributes of the HUI Mark 2 (HUI2) and HUI Mark 3 (HUI3) would likely be affected by severity of diabetes and its complications or comorbidities. For example, amputation and peripheral neuropathy would presumably affect the mobility and self-care attributes of the HUI2 and the ambulation and dexterity attributes of the HUI3. Similarly, neuropathy and myopathy would likely affect the pain and discomfort attribute of the HUI2 and HUI3 and the dexterity attribute of the HUI3. Retinopathy would likely affect the vision attribute of the HUI3 and the sensation attribute of the HUI2. The emotion attributes of the HUI2 and HUI3 would be affected by diabetes itself and comorbid depression. Empirical evidence of the construct validity of the HUI2 and HUI3 in type 2 diabetes is, however, lacking at this time.

1.5.0 Construct Validity

There are several approaches that can be taken to assessing construct validity, one of which is referred to as the 'known' or 'extreme' groups approach. Using the known groups approach, individuals are divided into groups expected to differ in HRQL, according to an external criteria. Clinically important differences in HRQL scores should be observed between known groups if the instrument does, indeed, have construct validity in the target population. Interscale correlations between HRQL measures (i.e measures of the same construct) can also provide evidence of convergent construct validity. Evidence of validity is generated when two instruments that are intended to measure the same HRQL domain correlate. The accumulation of construct validity evidence in a variety of applications and contexts, using a variety of techniques adds confidence that a measure is valid in those uses.

The application of multi-attribute utility measures in diabetes has been relatively limited. Recently, however, several of these measures, specifically the EQ-5D or EuroQoL, Quality of Well-Being Scale – Self-Administered (QWB-SA), and 15-D, have been used in diabetes and evidence has been generated to support their use in the condition.(15;32-40) Since the burden of diabetes has generally been attributed to disease related factors(35-37), treatment burden(35;36;39) and comorbidities and complications(15;32-36;38;40), it is reasonable that these factors were used to form known groups in previous studies assessing the construct validity of multi-attribute utility measures in diabetes.(15;32-40)

1.6.0 Determinants of Health in Type 2 Diabetes

The health of Canadians is determined by a broad range of social, environmental, behavioural and disease-related factors. The contribution of the determinants of health to overall HRQL in type 2 diabetes, specifically, has been assessed in past research, but generally the focus has tended to be on demographic, clinical, treatment and disease-related factors, with less emphasis on behavioural and social determinants of health. A more holistic approach to studying the determinants of health in type 2 diabetes would provide a better understanding of the factors that influence the lives of individuals with the disease. As well, it would allow us to assess previously studied relationships, while controlling for important social determinants, such as stress, social relationships and access to healthcare.

1.7.0 Summary

Past research indicates that diabetes results in a burden on a broad range of health domains, and HRQL deficits in people with diabetes are worsened by the presence of complications and comorbidities. However, the impact of important social determinants of health should also be considered. Generic measures of HRQL provide information that can be compared across disease states and permit comparisons of the burden associated with various diseases on multiple dimensions of HRQL, which may provide useful data for policy and resource allocation decisions. Before generic measures are employed to assess HRQL in a given disease, it is important that construct validity is assessed in that particular disease. Once evidence of construct validity has been accumulated, generic measures of HRQL can be applied to studies of HRQL in particular diseases, such as assessing the importance of determinants of health in type 2 diabetes.

1.8.0 Objectives

The objectives of this program of research were (1) to generate initial evidence of the construct validity of three generic measures of HRQL (specifically, the RAND-12 and Health Utilities Index Mark 2 and Mark 3) in type 2 diabetes and (2) to assess the importance of a broad range of determinants of health in type 2 diabetes at the population level.

1.9.0 Program of Research

A series of four papers contributed to the overall study goals. The initial two studies (Chapters 2 and 3) involved a sample of rural Albertans with type 2 diabetes who were enrolled in a controlled intervention study to improve outcomes in type 2 diabetes.(41) Data from the intervention study were used to evaluate the construct validity of the RAND-12, HUI2 and HUI3 (Chapter 2), and allowed for a comparison of the HUI2 and HUI3 in type 2 diabetes (Chapter 3). The final two studies (Chapters 4 and 5) involved a representative population-based sample of community dwelling Canadians with type 2 diabetes. The first population-based study (Chapter 4) provided additional evidence of the construct validity of the HUI3 in type 2 diabetes, and did so in a nonclinical setting. After having accumulated evidence of the construct validity of the HUI3 in type 2 diabetes, the final population-based study (Chapter 5) used a holistic determinants of health framework to assess sources of heterogeneities in HRQL in the general Canadian community dwelling population with type 2 diabetes.

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Chapter 2 - Construct Validity of the RAND-12 and Health Utilities Index Mark 2 and 3 in Type 2 Diabetes[1]

2.1.0 Introduction

When measuring health-related quality of life (HRQL) in any condition, it is essential that the instruments used are valid in the population under study. Validity can be defined as the extent to which an instrument measures the property it is intended to measure.(1) A common approach to assessing validity is to establish *a priori* hypotheses on the relationship between HRQL scores and subgroups of patients known to differ in disease severity. Further, it is often recommended that assessment of HRQL can be more informed by using a combination of specific and generic measures of HRQL, with each approach having advantages. Disease-specific measures have the advantage of focusing on the particular problems associated with the disease under study.(2) Such measures may be better able to identify functional impairments arising from the illness under study and may be more sensitive to small changes in health resulting from treatment than generic measures.(3)

Despite concerns of decreased sensitivity, generic measures of HRQL have an advantage over disease specific measures in that they permit comparisons of the impact of various diseases on multiple dimensions of HRQL, which may provide useful data for policy and resource allocation decisions.(3) Generic measures can be classified into health status profiles and preference-based index measures.(3) Preference-based measures, such as the

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Health Utilities Index, are based upon decision theory and economics and reflect preferences for alternative health outcomes.(3) Preference-based measures can integrate morbidity and mortality, and allow incorporation of HRQL into economic evaluations, in the form of quality-adjusted life years (QALYs).

Diabetes places a substantial burden on individuals with the disease and their families, arising from the condition itself, its treatment and complications associated with the disease.(4-10) Diabetic complications, such as retinopathy, nephropathy, neuropathy, cardiovascular disease, stroke and peripheral vascular disease, result in significant morbidity and mortality.(4-12) The morbidity burden of diabetes can be associated with impairment on many dimensions of HRQL, including social, cognitive, role and physical functioning, emotional well-being, general perceptions of health and pain.(4;10;12-15) Self-reported HRQL is an important outcome to assess in diabetes because clinical measures, such as glycosylated hemoglobin (HbA1c), may fail to capture the overall impact of the disease.

A great deal of research has assessed the ability of disease-specific and generic measures of HRQL to discriminate between subgroups of individuals with diabetes expected to have different levels of HRQL. From this literature, several trends have emerged. First, the presence and severity of complications has been associated with clinical depression and anxiety, impairment on all subscales of the SF-36 and Diabetes Quality of Life scale, and lower scores on the Nottingham Health Profile in individuals with type 1 or type 2 diabetes.(5-7;16) There is also evidence that increased intensity of treatment (i.e.

progressing from diet to oral medications and finally to insulin) in individuals with type 2 diabetes is associated with lower levels of HRQL, measured using either disease-specific or generic instruments.(6;7;9;16) This relationship is likely attributable to the fact that more intense treatment is associated with more advanced disease, but may also reflect increased treatment burden.

Past research has also produced a number of inconsistencies. Longer duration of diabetes has been associated with lower levels of HRQL in some studies(5;9;17;18), while other studies have failed to find this association, even when the same instrument was used.(19;20) Importantly, poor glycemic control has not been consistently associated with lower levels of HRQL in individuals with diabetes, particularly when generic measures are used. Several studies have explored the relationship between SF-36 scores and glycemic control and rarely has an association between HbA1c and HRQL been found.(20) Conversely, using generic measures of emotional distress, poor glycemic control has been associated with higher levels of displeasure, depression, tension and fatigue in individuals with type 2 diabetes.(21) Similarly, Testa et. al. found that improved glycemic control was related to lower levels of symptom distress and higher levels of general perceived health, overall quality of life rating, mental health and cognitive function, using a series of visual analog scales and over 50 items reflecting symptom distress, not necessarily specific to diabetes.(22)

While a number of studies have used generic health profiles to assess HRQL in diabetes, past research exploring preference-based measures in diabetes is limited. The comparison of burden across disease states using preference-based measures may provide useful data for policy and resource allocation decisions.(3) A review of the literature produced a limited number of studies which used preference-based measures in diabetes.(23-32) Past research into HRQL in diabetes using the Health Utilities Index Mark 2 or 3 (HUI2 or HUI3) is sparse. Thus, there remains a need for further investigation of the HUI2 and HUI3 in diabetes to determine if these measures adequately capture the HRQL burden of the disease.

The RAND-12 is a generic profile measure of HRQL that has not been used to study HRQL in diabetes. Many studies have applied the SF-36 in diabetes, but differences in the scoring algorithms of the SF-36 and RAND-12, number of items and domains captured by the instruments attenuates the generalization of results between the two instruments. Thus, further investigation of the measurement properties of the RAND-12 in diabetes is warranted.

The objective of this study was to assess the cross-sectional construct validity of the RAND-12, HUI2 and HUI3 in type 2 diabetes, using the known groups approach. In order to meet the study objective, the ability of each instrument to distinguish between subgroups of individuals, representative of more and less advanced diabetes or differing levels of disease severity, was determined.

2.2.0 Research Design and Methods

2.2.1 Study Design

The assessment of the construct validity of the RAND-12, HUI2 and HUI3 was conducted as part of a larger, prospective, controlled study of an intervention to improve care for individuals with type 2 diabetes in rural communities in Alberta, Canada.(33) Ethical approval for the larger study was obtained through the University of Alberta Health Research Ethics Board Panel A.

2.2.2 Sample

Three hundred and ninety-four individuals with type 2 diabetes participated in the larger study. In order to be included in the study, subjects had to have type 2 diabetes, live within the control or intervention region, consent to baseline measurements, be sufficiently literate in English to answer questionnaires and be willing to participate in follow-up visits. Subjects were excluded if they were discovered not to have type 2 diabetes, had a life-expectancy of less than six months, declined enrollment or were unable or unwilling to give informed consent. Diabetes health care professionals, diabetes education programs, community pharmacists or primary care physicians referred subjects into the study. As well, some subjects entered the study through self-referral. Of the 394 subjects originally enrolled in the study, 372 completed baseline HRQL questionnaires. All HRQL measures were self-administered, self-completed and submitted via mail or at the time of a study visit.

2.2.3 Measures

2.2.3.1 Clinical

Blood samples for HbA1c were all drawn in labs in Northern Alberta and the analysis of samples was carried out in a central lab. Data on treatment regimen for diabetes and duration of diabetes was self-reported by study subjects.

2.2.3.2 Health Related Quality of Life Measures

The RAND-12, HUI2 and HUI3 were used to measure the disease burden of patients. Both HRQL measures were self-administered, self-completed at the time of a study visit or submitted via mail.

2.2.3.2.1 RAND-12 Health Status Inventory

The RAND-12 contains 12 items taken from the eight scales of the RAND-36 Health Status Inventory (RAND-36) (34)and measures physical and mental dimensions of HRQL (Appendix A). Six of the 12 items create the Physical Health Composite (PHC) and the remaining six items create the Mental Health Composite (MHC). Scoring of each scale uses a one-parameter Rasch model, based on item response theory. The PHC and MHC are norm-based standardized scores, with a mean of 50 and standard deviation of 10 (i.e. T-Scores) in the general United States Population.(34)

2.2.3.2.2 Health Utilities Index Mark 2 (HUI2) and Health Utilities Index Mark 3 (HUI3)

The HUI2 and HUI3 are preference-based measures of HRQL that use multi-attribute utility functions to assign valuations to different health states.(35) Health states are defined by classification systems that includes a set of dimensions or attributes of health status, with a number of different levels for each attribute. Using a single questionnaire or instrument, self-reported health status according to both the HUI2 and HUI3 can be determined.(35) This study used a 15-item self-administered version with a four week recall period (i.e. the HUI2315Q4W).(36)

In the HUI2 system, health status is characterized by six attributes: sensation (hearing, vision, speech), mobility, emotion, cognition, self-care, and pain (Appendix B).(35) Fertility is a seventh attribute in the system, but was not included in this study.(35) Each of the remaining six attributes has four or five different levels in the HUI2 system. Levels on an attribute range from highly impaired (eg. for cognition unable to learn and remember) to normal. The levels and attributes combine to describe 24,000 unique HUI2 health states. Global scores on the HUI2 range from -0.03 to 1.0, with -0.03 representing the utility of the worst possible HUI2 health state, 0.0 representing dead and 1.0 representing perfect health.(35;36)

In the HUI3 system, eight attributes including vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain and discomfort define health status (Appendix C). Each attribute has five or six levels, creating 972,000 unique HUI3 health states.(35) Overall scores on the HUI3 range from -0.36 to 1.0, with -0.36 representing the utility of the worst possible HUI3 health state, 0.0 representing dead and 1.0 representing perfect health. Differences of 0.03 or more on the HUI2 or HUI3 overall scores may be considered important.(36)

In addition to overall scores, single attribute utility scores can be obtained for each attribute of the HUI2 and HUI3, ranging from 0.0 to 1.0, with a score of 0.0 representing the lowest level of functioning (e.g for the vision attribute, being blind would be scored 0.0), and 1.0 representing full functional capacity on that attribute. Differences of 0.05 or more on the single attributes may be considered clinically important.(36) The morbidity burden on each single attribute can also be captured by the distribution of individuals at each level on the attribute.

The utilities assigned to the health states and single attributes of the HUI2 and HUI3 were calculated from their respective scoring functions. The scoring functions themselves were originally derived from directly measuring the utility of a variety health states, based on the standard gamble approach.(35;36)

2.2.4 Data Analysis

As an assessment of construct validity of the RAND-12, HUI2 and HUI3, tests of statistical significance were used to determine the ability of each summary score to discriminate between groups representative of differing disease severity. Disease severity or advancement was defined in terms of treatment intensity of diabetes, duration of diabetes, absenteeism from work due to diabetes and glycemic control. Treatment of diabetes was used as an indicator because the Canadian Diabetes Association recommended a step-wise approach to the management of type 2 diabetes starting with diet alone, then progressing to oral hypoglycemics and, finally, to insulin in the guidelines that were current at the time of the study.(37) Thus, individuals treated with insulin were presumed to have the most advanced disease, while individuals managed using diet alone were presumed to have the least advanced disease. To test the ability of the instruments to distinguish between groups with differing levels of glycemic control and duration of diabetes, subjects were dichotomized on each variable using a median split. For absenteeism from work due to diabetes, individuals were dichotomized as haven taken no days or one or more days off work for diabetes.

For all scales, it was hypothesized that groups with more advanced or severe diabetes would have lower scores. The cross-sectional construct validity of the HUI2 and HUI3 was further assessed by determining the ability of the single attributes to distinguish between individuals with varying degrees of disease severity or advancement. For the HUI2, we hypothesized that individuals with more severe or advanced disease would have lower single attribute utility scores for sensation, mobility, emotion, self-care and pain. Similarly, we hypothesized that individuals with more advanced or severe diabetes would have lower HUI3 single attribute utility scores for ambulation, dexterity, pain, vision and emotion. No differences were expected to be observed for cognition attributes of the HUI2 and HUI3, and speech or hearing attributes of the HUI3.

2.2.4.1 Statistical Significance Testing

For comparisons between two groups (e.g. above and below median duration of diabetes) we employed t-tests; comparisons by treatment type were tested using ANOVA. When the distribution of the dependent variables did not follow a normal distribution, we also employed nonparametric tests of significance; in all cases these yielded the same conclusions, so we chose to report only the parametric results.

Interscale correlations were calculated to assess further the construct validity of the RAND-12, HUI2 and HUI3. Spearman's Rho was used to test the strength of association between PHC-12 and MHC-12 of the RAND-12 and the overall and single attribute utility scores of the HUI2 and HUI3. Correlations of greater than 0.50 were considered to be strong, and between 0.30 and 0.49 were considered moderate and less than 0.30 was considered to be weak.(38)

We hypothesized that the PHC would be strongly correlated with the overall score for the both the HUI2 and HUI3. Further, we hypothesized strong correlations between the PHC and the mobility, self-care and pain single attribute utility scores of the HUI2. For the HUI3, strong correlations were hypothesized between the PHC and the ambulation, dexterity and pain single attribute utility scores of the HUI3. Finally, it was hypothesized that MHC would be strongly correlated with the overall score and the emotion single attribute utility scores of the HUI2 and HUI3. A p-value of less than 0.05 was considered to be statistically significant for all comparisons; no adjustments were made for multiple testing as this analysis was considered to be exploratory pilot work in a relatively small sample size. More importantly, the clinical importance or magnitude of the observed differences between groups was considered.

2.3.0 Results

The majority of the sample was female, currently married and had not completed high school (Table 2-1). The median duration of diabetes of 5.0 years (Interquartile Range: 2.0 – 12.00). The most common treatment was oral medication, although a substantial proportion of the sample (27.2%) were receiving insulin. The PHC was slightly lower than the MHC. Both composites were approximately one-half of a standard deviation below the general United States population norm of 50 (Table 2-1). The average overall HUI2 score for the study sample was 0.78 ± 0.18 and 0.64 ± 0.30 for the HUI3.

The percentage of the study sample with HRQL data missing ranged from a low of 1.1% (n=4) for the self-care attribute of the HUI2 to a high of 15.6% (n=58) for the HUI2 overall score. If an individual's level was missing for any of the HUI attributes, the overall score would be missing. Of the study subjects who had completed the baseline questionnaires, subjects missing the PHC, MHC, HUI2 and HUI3 overall scores were statistically significantly older and had lower incomes than subjects with complete data.

Of the clinical variables used to characterize the sample, total cholesterol was significantly higher for subjects with missing HUI2 and HUI3 overall scores, but not for the RAND-12 composites. For the variables used to separate subjects into known groups, subjects with missing HUI2 and HUI3 tended to have more intensive treatment of their diabetes, i.e. they were more likely to use insulin and/or oral medications than to be managed on diet alone. Finally, subjects missing the PHC and MHC were more likely to have taken days off work for diabetes than subjects with scores on these measures.

2.3.1 RAND-12 Scores

As hypothesized, the PHC was lower for groups expected to have more severe or advanced diabetes (Table 2-3). These differences reached statistical significance for a number of comparisons. The PHC was lower for individuals whose diabetes was managed with insulin than individuals whose diabetes was managed by diet alone or diet and oral medication. The absolute magnitude of these differences was approximately one-half of a standard deviation (i.e., an effect size of 0.5, which would be considered moderate and perhaps meaningful). Differences in the PHC were observed between individuals above and below the median duration of diabetes and were of a similar magnitude, again representing a moderate effect size. Though the number of employed individuals who reported an absenteeism from work due to diabetes was small (n=9), the HRQL burden of this group was substantial. Differences in the PHC between individuals who were and were not absent from work was 13.47 ($p < 0.01$), representing a large effect size. The hypothesis pertaining to glycemic control was not supported by the analysis.

The MHC decreased with increased treatment intensity of diabetes (Table 2-3), although the difference only achieved statistical significance for the comparison between individuals whose diabetes was managed by diet alone compared to those on insulin, representing a small to moderate effect size. The magnitude of the difference in the MHC was small but statistically significant for the comparison of individuals above and below the median duration of diabetes, although the effect size was small. As with the PHC, a moderate to large effect size (0.74, $p < 0.01$) was also observed between the MHC scores of individuals who had and had not been absent from work due to diabetes. Differences in the MHC were not statistically significant for the comparison of individuals above and below the median HbA1c.

2.3.2 HUI2 and HUI3

Overall scores for the HUI2 and HUI3 were significantly higher for individuals managed with diet alone (Table 2-4), compared to individuals whose diabetes was managed with insulin ($p < 0.05$ for each). The magnitude of the difference was larger for the HUI3 than for the HUI2 (0.10 vs 0.06), though both differences are clearly clinically important. HUI2 and HUI3 overall utility scores were statistically significantly higher for individuals who had diabetes less than or equal to five years (Table 2-5). The magnitude of this difference was 0.07 for both global utilities, again indicating a clearly important difference between groups. The difference in overall HUI3 score between individuals who did and did not report absence from work due to diabetes was substantial (0.19), but failed to reach statistical significance (Table 2-6). For individuals above and below the median HbA1c, no statistically significant or clinically important differences were found for overall or single attribute utility scores for the HUI2 or HUI3.

For the single attribute utility scores, several hypotheses were supported by the data. First, differences in the mobility and self-care on the HUI2 and vision, ambulation and dexterity on the HUI3 were statistically significant for individuals whose diabetes was managed with diet alone or oral medication each compared to individuals whose treatment regimen included insulin (Table 2-4). The emotion attribute of the HUI2 was higher for individuals treated with diet alone compared to oral medications (0.94 ± 0.09 vs 0.91 ± 0.14, $p<0.05$) and for individuals treated with diet alone compared to insulin (0.94 ± 0.09 vs 0.86 ± 0.19, $p<0.01$). Similarly, the emotion attribute of the HUI3 was higher for individuals treated with diet alone compared to insulin (0.93 ± 0.12 vs 0.85 ± 0.23, $p<0.01$). Again, the magnitude of the difference in the emotion attribute according to treatment regimen indicated clinically important differences between groups.

For the comparison between individuals whose duration of diabetes was above and below the median, the majority of hypotheses about the single attribute utilities were supported (Table 2-5). Individuals with diabetes for more than five years had significantly lower scores on the sensation, pain and mobility attributes of the HUI2. As well, for the HUI3, individuals with diabetes more than five years had lower scores on the vision, ambulation, dexterity and pain attributes. It should be noted, however, that the magnitude of the differences were relatively small for several comparisons, with the exception of the pain and vision attributes. As hypothesized, differences in cognition, speech and hearing attributes did not reach statistical significance and would not be considered clinically important.

Among individuals in the workforce, those who had required time off work due to diabetes demonstrated statistically significant or clearly important burdens on the HUI2 and HUI3 single attribute utility score (Table 2-6). The magnitude of this difference in the emotion attribute was large for both the HUI2 (0.06) and for the HUI3 (0.08), though the difference in the HUI2 emotion attribute failed to reach statistical significance. For absenteeism from work due to diabetes, the pain attribute demonstrated clinically important differences for both. Interestingly, the magnitude of the difference was substantially larger for the HUI3 (0.24) than the HUI2 (0.05), with the difference in HUI2 score failing to reach statistical significance. For the HUI2, scores on the self-care attribute were statistically significantly lower for individuals who had taken time off work (0.98 ± 0.05) than those who had not (1.00 ± 0.02, $p < 0.05$), but the magnitude of this difference was small. While the vision attribute of the HUI3 demonstrated statistically significantly lower scores in individuals who had taken time of work, the magnitude of this difference (0.04) was such that it was not clearly clinically important.

2.3.3 Interscale Correlations

As hypothesized, the PHC was strongly correlated with the HUI2 and HUI3 overall score and the pain single attribute scores (Table 2-7 and Table 2-8). Contrary to the hypotheses, the magnitude of the correlations between the PHC and mobility, self-care, ambulation and dexterity attributes were moderate (i.e. Spearman's rho < 0.05), rather than strong. Moderate correlations were also observed between the emotion attributes and the PHC, a finding that could be in part reflective of the strong correlation between the PHC and MHC in this patient population ($r = 0.641$, $p < 0.001$). Hypotheses for the MHC were supported as strong correlations were found between the MHC, overall HUI2 and HUI3 scores and emotion attributes, but were weak to moderate for the remaining attributes.

2.4.0 Discussion

As hypothesized, the HRQL scores were generally lower for individuals expected to have more severe or advanced diabetes. These differences achieved statistical significance and clinical importance for the PHC and MHC according to treatment regimen, duration of diabetes and absenteeism from work due to diabetes. Similarly, HUI2 and HUI3 overall scores tended to be lower for individuals with more severe or advanced diabetes and reflected clearly meaningful differences for many comparisons. The magnitude of the differences in overall scores were larger for the HUI3 for treatment regimen and absenteeism from work than overall HUI2 scores. The magnitude of the differences was also larger than those observed for the RAND-12, perhaps indicating a higher degree sensitivity of the HUI3 to the disease burden of type 2 diabetes. While this could indeed be the case, it is not clear from this analysis precisely from where the increased sensitivity of the HUI3 relative to the HUI2 arose. Differences in the range of possible scores, number of levels per attribute and the attributes themselves could all contribute to the general trend of lower overall HUI3 utility scores relative to the HUI2 overall utility scores. This issue and the associated implications are complex and warrants further, in depth research.

Support for the HUI2 single attributes varied across known group comparisons. More intense treatment was associated with lower HUI2 scores for mobility, emotion and self-care single-attribute utility scores. Differences in the mobility and self-care attributes of the HUI2 could likely be related to the presence of complications, such as neuropathy or amputations. The pain attribute of the HUI2 was significantly associated with duration of diabetes. The difference in score between individuals above and below the median duration of diabetes was of a magnitude that would be considered clinically important. The difference in HUI2 pain scores for individuals who were and were not absent from work due to diabetes would be considered clinically important, again demonstrating the ability of the HUI2 pain attribute to capture varying levels of HRQL burden in type 2 diabetes.

Similarly, a number of hypotheses for the single attribute utilities of the HUI3 were supported by the data. Longer duration and more advanced disease were hypothesized to affect the ambulation attribute of the HUI3. It was found that individuals treated with insulin and whose duration of diabetes exceeded the median did, indeed, have lower scores on the ambulation attributes. These groups were representative of individuals in which complications would be more prevalent. Similarly, the presence of neuropathy was hypothesized to affect the dexterity attribute of the HUI3, which was supported by lower scores for individuals treated with insulin and who had a longer duration of diabetes. It should be noted, however, that the magnitude of the difference between individuals above and below the median duration of diabetes was small for the dexterity attribute. Finally, the prevalence of retinopathy would be expected to increase with disease progression and would be reflected in the vision attribute of the HUI3. Lower scores on the vision attribute were observed for individuals treated with insulin or whose duration of diabetes of was greater than five years. The magnitude of the difference in disease burden for individuals who had and had not been absent from work due to diabetes was particularly large.

Differences in mental health were detected by the emotion attributes of the HUI2, HUI3 and the MHC. The relationship between the mental dimension of HRQL and diabetes has been revealed in past research. A recent meta-analysis which examined the relationship between depression and diabetes and found that individuals with type 2 diabetes were 2.9 times as likely (95% CI = 1.6-5.5) as controls without diabetes to have depression.(14) Thus, a relationship between disease severity and the emotion attribute would not be unexpected. The observed difference in HUI emotion single attribute scores between individuals managed with diet alone and with insulin was large and clearly important for both the HUI2 and HUI3. The results for the MHC corroborated the findings for the emotion attributes, decreasing the likelihood that the differences in the emotion attribute arose from chance variation, though the magnitude of differences in scores between groups were somewhat smaller on the MHC. A strong correlation was observed between the emotion attribute of the HUI3 and the MHC, further supporting the construct validity of the measures. The correlation between the HUI2 emotion attribute and the MHC was moderate, a finding perhaps related to difference in the type of emotion captured by the HUI2 and HUI3. In the HUI2, the emotion attribute captures feelings of anxiety(36), while the HUI3 emotion attribute is more related to happiness, depression or sadness.(35)

In addition to similarities in the findings for mental health, other similarities in finding for the HUI2, HUI3 and RAND-12 were observed. The PHC and HUI3 overall scores were significantly lower for individuals above the median duration of diabetes. Furthermore, differences between individuals above and below the median duration were found on the pain, ambulation, and dexterity single attribute utilities, which relate to physical function. Similarly, the HUI2 detected differences on the mobility and pain attributes, though the overall HUI2 score failed to reach statistical significance. Finally, a similar pattern emerged for treatment of diabetes, in that several of the single attribute utility scores were lower for attributes reflecting physical functioning, such as ambulation and dexterity for the HUI3 and the mobility and self-care attributes of the HUI2. These patterns were also reflected in the presence of moderate to strong correlations between PHC and ambulation, dexterity and pain single attribute scores of the HUI3 and pain scores of the HUI2.

Hypotheses regarding the relationship between poor glycemic control and HRQL were not supported by these data. The mean PHC and MHC for individuals above and below the median of HbA1c were similar, suggesting that either the RAND-12 is not sensitive enough to detect differences between these groups, a result similar to previous research using other generic measures of HRQL in diabetes, or that the relationship between glycemic control and HRQL is either weak or nonlinear. No differences were noted on the overall and single attribute utility scores of the HUI2 or HUI3 for individuals above and below the median of HbA1c. Again, this suggests either a lack of sensitivity of the instruments or a weak or nonlinear relationship between HRQL and glycemic control.

Although these results lend support to the construct validity of the RAND-12, HUI2 and HUI3 in type 2 diabetes, a number of study limitations should be recognized. First, the number of individuals for which HRQL data was missing was, in some cases, substantial, and statistically significant differences between individuals with complete and missing data for the various HRQL measures were found. It is unclear how these differences would affect study results on construct validity. Individuals missing HRQL data were older and had lower socio-economic status. Because all analyses presented herein were univariate comparisons, it is possible that this systematic absence of data would weaken several of the observed relationships. Further assessment of the impact of missing data and imputation methods are planned.

Data on treatment for diabetes was based on self-report and could potentially be a study limitation. However, a high level of agreement was observed when this data was compared to data obtained through a formal medication history taken by research coordinators for these patients.(39) Also, the presence of complications, which have been associated with HRQL in diabetes in the past(28), was not assessed directly. Instead, this study used treatment intensity and duration of diabetes as indirect measures of disease severity, with the assumption that more prolonged and advanced diabetes would be associated with more complications.

Further research using the RAND-12, HUI2 and HUI3 in diabetes is warranted, as these measures appeared to be sensitive to disease severity, as a surrogate measure of the presence of complications. The various single attributes of the HUI2 and HUI3 capture important differences in health status in type 2 diabetes. In this sample, it appears that the HUI2 did not offer any specific advantage over the HUI3. In fact, it did appear that the overall utility scores generated by HUI3 may be more able to capture the burden associated with diabetes, and, thus, may be preferable to the HUI2 when examining global health status. When examining specific attributes of HRQL, differences in the content of the single attributes of the HUI2 and HUI3 make the choice between instrument versions less clear. These differences should be considered when evaluating specific dimensions of HRQL in type 2 diabetes, as specific attributes from each system could provide valuable information. While both instruments assess pain and emotion, for instance, the nature of pain and emotion is substantively different between the HUI2 and HUI3. Thus, the information provided by utilizing both the HUI2 and HUI3 single attribute utility scores could be considered complementary, rather than redundant. Future research should explore the relationships between these HRQL measures and diabetic complications directly, and the responsiveness of these measures to detect within person change over time.

2.5.0 Conclusion

In conclusion, applying generic measures of HRQL to diabetes is important in order to make comparisons between disease states and individuals with and without disease. The PHC and MHC of the RAND-12 discriminated between individuals anticipated to have differing levels of disease severity or advancement, for a number of comparisons. Evidence of the validity of preference-based measures in diabetes would be helpful in future analyses aiming to inform resource allocation decisions. Differences in overall HUI2 and HUI3 scores achieved statistical significance for a number of comparisons and clearly important differences between groups were noted. Similarly, single attribute utilities of HUI2 and HUI3 seemed sensitive to the dimensions of HRQL likely to be affected by diabetes and its complications. HbA1c, a physiologic measure of average glycemic control was not related to any of the generic HRQL scores and may not adequately reflect individuals' overall physical and mental health. We believe the results of this study contribute evidence of cross-sectional construct validity of the RAND-12, HUI2 and HUI3 in diabetes.

Table 2-1: Demographic, Clinical and HRQL Characteristics (n=372)

Age - Mean (SD)	62.3 (12.5)
Sex, Males - n (%)	164 (41.6)
Income - n (%)	
less than $5,000	32 (8.1)
$5000 to $19999	122 (31.0)
$20,000 to $39,999	90 (22.8)
greater than $40,000	85 (21.6)
Marital status, Currently married - n (%)	227 (57.6)
English as first language, Yes - n (%)	269 (68.3)
Graduated high school, Yes - n (%)	120 (30.5)
Main activity - n (%)	
Retired	154 (39.1)
Caring for family and working for pay	64 (16.2)
Working for pay	42 (10.7)
Caring for family	36 (9.1)
Recovering from illness	31 (7.9)
Duration of diabetes (years) – Median (Interquartile Range)	5.0 (2.0 – 12.0)
HbA1c – Median (Interquartile Range)	0.07 (0.06 – 0.08)
Body Mass Index - Mean (SD)	32.9 (6.9)
Total Cholesterol - Mean (SD)	4.96 (0.99)
Systolic Blood Pressure - Mean (SD)	131 (18.6)
Diastolic Blood Pressure - Mean (SD)	76 (11.5)
Treatment of Diabetes - n (%)	
No treatment with oral hypoglycemics or insulin	69 (17.5)
Treatment with oral hypoglycemic	190 (48.2)
Treatment with insulin alone or with oral hypoglycemics	107 (27.2)

Table 2-2: Descriptive statistics for HRQL measures

HRQL Measure	N	Missing N (%)	Min	Max	Mean	SD	Median	IQR
RAND-12 MHC	323	49 (13.2)	19.39	64.60	44.84	10.24	45.46	36.30 – 53.36
RAND-12 PHC	323	49 (13.2)	8.98	60.69	43.48	10.81	45.22	35.32 – 52.35
HUI2 Overall	312	60 (16.1)	0.12	1.00	0.78	0.18	0.82	0.72 – 0.92
HUI2 Sensation	331	41 (11.0)	0.00	1.00	0.80	0.19	0.87	0.65 – 0.87
HUI2 Mobility	357	15 (4.0)	0.34	1.00	0.94	0.13	1.00	0.92 – 1.00
HUI2 Emotion	363	9 (2.4)	0.00	1.00	0.90	0.15	1.00	0.86 – 1.00
HUI2 Cognition	361	11 (3.0)	0.66	1.00	0.93	0.08	1.00	0.86 – 1.00
HUI2 Self-care	366	7 (1.9)	0.00	1.00	0.98	0.09	1.00	1.00 – 1.00
HUI2 Pain	359	13 (3.5)	0.00	1.00	0.87	0.21	0.95	0.95 – 1.00
HUI3 Overall	317	55 (14.8)	-0.25	1.00	0.64	0.30	0.70	0.49 – 0.91
HUI3 Vision	353	19 (5.1)	0.00	1.00	0.90	0.15	0.95	0.95 – 0.95
HUI3 Hearing	353	19 (5.1)	0.00	1.00	0.90	0.24	1.00	1.00 – 1.00
HUI3 Speech	354	18 (4.8)	0.41	1.00	0.97	0.09	1.00	1.00 – 1.00
HUI3 Ambulation	357	15 (4.0)	0.16	1.00	0.92	0.15	1.00	0.83 – 1.00
HUI3 Dexterity	365	7 (1.9)	0.20	1.00	0.96	0.12	1.00	1.00 – 1.00
HUI3 Emotion	365	7 (1.9)	0.00	1.00	0.88	0.20	0.91	0.91 – 1.00
HUI3 Cognition	361	11 (3.0)	0.32	1.00	0.90	0.15	1.00	0.92 – 1.00
HUI3 Pain	364	8 (2.2)	0.00	1.00	0.81	0.25	0.92	0.77 – 1.00

Table 2-3: Comparison of MHC and PHC scores between subgroups

	n	Mean (SD) MHC	Mean (SD) PHC
Treatment Regimen for Diabetes			
Group 1 - Diet only	62-64	46.87 (10.89) †	45.18 (12.02) ††
Group 2 - Oral medication without insulin	160-166	45.00 (9.58)	44.32 (9.93) ‡
Group 3 - Insulin with or without oral medication	86-90	42.83 (10.75)	40.28 (10.97)
Duration of Diabetes			
Less than or equal to 5 years	163-168	46.18 (9.94)*	45.62 (10.48)***
Greater than 5 years	136-144	43.56 (10.20)	41.04 (10.64)
Glycemic Control			
HbA1c $\leq$7.0	159-164	44.88 (10.18)	44.17 (10.72)
HbA1c > 7.0	144-150	44.72 (10.43)	42.55 (11.03)
Days off Work for Diabetes			
No days off work in prior 6 months	91-92	48.85 (8.46)**	48.22 (9.01)**
One or more days off work in prior 6 months	7-8	34.70 (12.62)	37.79 (11.16)

† $p < 0.05$ for comparison between Group 1 and Group 3
†† $p < 0.01$ for comparison between Group 1 and Group 3
‡ $p < 0.01$ for comparison between Group 2 and Group 3
* $p < 0.05$
*** $p < 0.001$
** $p < 0.01$

Table 2-4: Comparison of treatment regimen for diabetes based on mean (SD) HUI2 and HUI3 scores

Variable	**Group 1 - Diet Only (n=63-68)^{A}**	**Group 2 - Oral Medication (n=165-188)^{A}**	**Group 3 -Insulin (n=80-105)^{A}**	**Difference Between Groups^{B}**
HUI2 overall utility	0.80 (0.18) †	0.78 (0.16)	0.74 (0.20)	0.06
HUI2 Single Attribute Utility Scores				
Sensation	0.80 (0.19)	0.80 (0.20)	0.81 (0.17)	0.01
Mobility	0.96 (0.09) ††	0.95 (0.12) ‡	0.91 (0.16)	0.05
Emotion	0.94 (0.09)*	0.91 (0.14)	0.86 (0.19) ††	0.08
Cognition	0.94 (0.08)	0.93 (0.08)	0.92 (0.08)	0.02
Self-Care	0.99 (0.03)	0.99 (0.04) ‡	0.96 (0.15)	0.03
Pain	0.87 (0.22)	0.89 (0.19)	0.85 (0.25)	0.04
HUI3 overall utility	0.69 (0.30) †	0.64 (0.29)	0.59 (0.30)	0.10
HUI3 Single Attribute Utility Scores				
Vision	0.94 (0.08)	0.91 (0.14)	0.87 (0.19)	0.07
Hearing	0.90 (0.25)	0.88 (0.25) ‡	0.94 (0.20)	0.06
Speech	0.98 (0.09)	0.97 (0.10)	0.98 (0.08)	0.01
Ambulation	0.95 (0.13) ††	0.93 (0.14) ‡	0.89 (0.18)	0.06
Dexterity	0.97 (0.12) ††	0.97 (0.09) ‡	0.93 (0.17)	0.04
Emotion	0.93 (0.12) ††	0.89 (0.20)	0.85 (0.23)	0.08
Cognition	0.91 (0.14)	0.90 (0.16)	0.90 (0.15)	0.01
Pain	0.80 (0.28)	0.83 (0.20)	0.75 (0.31)	0.08

A n varied depending on number of subjects with missing data for each global and single attribute utility
B Difference between groups with largest and smallest utility scores.
† $p < 0.05$ for comparison between Group 1 and Group 3
†† $p < 0.01$ for comparison between Group 1 and Group 3
‡ $p < 0.05$ for comparison between Group 2 and Group 3
* $p < 0.05$ for comparison between Group 1 and Group 2

Table 2-5: Comparison of individuals above and below median duration of diabetes using mean (SD) HUI2 and HUI3 scores

Variable and Category	**Duration of Diabetes ≤ 5 Years (n=165-184)[A]**	**Duration of Diabetes > 5 Years (n=135-168)[A]**	**Difference Between Groups**
HUI2 overall utility**	0.81(0.15)	0.74 (0.20)	0.07
HUI2 Single Attribute Utility Scores			
Sensation*	0.82 (0.17)	0.78 (0.21)	0.04
Mobility***	0.96 (0.10)	0.92 (0.15)	0.04
Emotion	0.92 (0.11)	0.89 (0.19)	0.03
Cognition	0.93 (0.09)	0.93 (0.08)	0.00
Self-Care	0.99 (0.04)	0.98 (0.12)	0.01
Pain**	0.90 (0.17)	0.85 (0.24)	0.05
HUI3 overall utility**	0.67 (0.29)	0.60 (0.29)	0.07
HUI3 Single Attribute Utility Scores			
Vision*	0.93 (0.11)	0.88 (0.18)	0.05
Hearing	0.90 (0.23)	0.89 (0.24)	0.01
Speech	0.97 (0.10)	0.97 (0.09)	0.00
Ambulation***	0.94 (0.13)	0.90 (0.16)	0.04
Dexterity**	0.97 (0.10)	0.95 (0.13)	0.02
Emotion	0.90 (0.16)	0.87 (0.22)	0.03
Cognition	0.90 (0.17)	0.90 (0.14)	0.00
Pain*	0.84 (0.22)	0.77 (0.28)	0.07

A n varied depending on number of subjects with missing data for each global and single attribute utility

** $p < 0.01$

* $p < 0.05$

*** $p \leq 0.001$

Table 2-6: Comparison of subjects who required and did not require days off work for diabetes in prior 6 months using mean (SD) HUI2 and HUI3 scores

Variable	**No days off work for diabetes in prior 6 months (n=86-95)** [A]	**One or more days off work for diabetes in prior 6 months (n=9)** [A]	**Difference Between Groups**
HUI2 overall utility	0.85 (0.12)	0.80 (0.195)	0.05
HUI2 Single Attribute Utility Scores			
Sensation	0.85 (0.13)	0.85 (0.16)	0.00
Mobility	0.99 (0.03)	0.99 (0.03)	0.00
Emotion	0.93 (0.09)	0.87 (0.12)	0.06
Cognition	0.95 (0.07)	0.97 (0.06)	0.02
Self-Care*	1.00 (0.02)	0.98 (0.05)	0.02
Pain	0.93 (0.16)	0.88 (0.19)	0.05
HUI3 overall utility	0.77 (0.23)	0.58 (0.35)	0.19
HUI3 Single Attribute Utility Scores			
Vision*	0.93 (0.10)	0.97 (0.03)	0.04
Hearing*	0.95 (0.16)	0.83 (0.26)	0.12
Speech	0.99 (0.04)	0.96 (0.11)	0.03
Ambulation	0.98 (0.05)	0.98 (0.06)	0.00
Dexterity	0.99 (0.04)	0.97 (0.05)	0.02
Emotion*	0.93 (0.11)	0.85 (0.12)	0.08
Cognition	0.94 (0.13)	0.96 (0.10)	0.02
Pain*	0.87 (0.19)	0.63 (0.38)	0.24

A n varied depending on number of subjects with missing data for each global and single attribute utility

* $p < 0.05$

Table 2-7: Interscale Correlations for RAND-12 and HUI2^{A}

	PHC	MHC
Overall HUI2	**0.602****	**0.588****
Sensation	0.148*	0.221**
Mobility	**0.476****	0.279**
Emotion	0.391**	**0.609****
Cognition	0.293**	0.377**
Self-Care	**0.278****	0.179**
Pain	**0.608****	0.434**

A Bold type indicates a hypothesized Spearman's Rho of > 0.50
* $p < 0.05$
** $p < 0.01$

Table 2-8: Interscale Correlations for RAND-12 and HUI3[A]

	PHC	MHC
HUI3	**0.643****	**0.604****
Vision	0.068	0.063
Hearing	0.122*	0.187**
Speech	0.174**	0.239**
Ambulation	**0.476****	0.278**
Dexterity	**0.322****	0.199**
Emotion	0.436**	**0.642****
Cognition	0.315**	0.447**
Pain	**0.648****	0.453**

A Bold type indicates a hypothesized Spearman's Rho of > 0.50
* $p < 0.05$
** $p < 0.01$

2.6.0 References

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Chapter 3: A Comparison of the Health Utilities Index Mark 2 and Mark 3 in Type 2 Diabetes[2]

3.1.0 Introduction

Diabetes mellitus affects approximately 4.2% of Canadians, 90% of whom have type 2 diabetes.(1) Despite an improved understanding of modifiable risk factors for type 2 diabetes (obesity, sedentary lifestyle and high fat diet), the prevalence and annual death rate of type 2 diabetes continue to rise. (2;3) Individuals who live with the disease have substantial morbidity burden arising from the condition, treatment and associated complications.(4-10) Type 2 diabetes affects many dimensions of health-related quality of life (HRQL), including social functioning, cognitive functioning, role functioning, physical functioning, emotional well-being, general perceptions of health and pain.(11-15) Self-reported HRQL is an important outcome to assess in diabetes because clinical measures, such as glycosylated hemoglobin (HbA1c), may fail to capture the overall impact of the disease.

General recommendations for assessing HRQL suggest the concurrent use of several types of measures, including specific measures, generic health profiles and preference-based measures, to capture a broad scope of HRQL.(16) A variety of HRQL measures are available to choose from, depending on the purposes of the measurement and the attributes of health that are important to measure. It is important to minimize respondent burden by choosing measures with appropriate content, in order to yield maximum data or information from relatively short questionnaires. Multi-attribute utility measures may be especially useful, as they can provide categorical information on each attribute, domain-specific scores and overall preference-based index scores. Generic measures may be able to reasonably capture condition-specific information on health status if the dimensions captured in the measure are congruent with those likely to be affected by the disease.(17)

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[2] A version of Chapter 3 has been previously published: Maddigan SL, Feeny DH, Johnson JA. A comparison of the Health Utilities Indices Mark 2 and Mark 3 in type 2 diabetes. *Medical Decision Making* 2003; 23: 489-501

The Health Utilities Indices (HUI) are a family of preference-based measures of HRQL. The summary scores of these measures may capture the overall picture of HRQL and the single attribute scores may provide additional information about the specific deficits associated with type 2 diabetes.(18) Past research into HRQL in diabetes using the Health Utilities Index Mark 2 (HUI2) or Health Utilities Index Mark 3 (HUI3) is sparse. Our preliminary research into the construct validity of those two measures generated initial evidence to support their use in type 2 diabetes, as they appeared to capture impairments related to overall HRQL and specific attributes of HRQL affected by severity of diabetes and unstable glycemic control.(19)

Important differences between the HUI2 and HUI3(20-22) could potentially lead to differences in their ability to capture HRQL deficits in type 2 diabetes. The objective of this analysis was to compare the extent to which the HUI2 and HUI3 detect differences associated with varying levels of disease severity or advancement and glycemic control in type 2 diabetes.

3.2.0 Research Design and Methods

3.2.1 Study Design and Sample

This analysis was conducted as part of a larger, prospective, controlled study of an intervention to improve care for 394 individuals with type 2 diabetes in rural communities in Alberta, Canada.(23) Briefly, two health regions (similar in terms of population, number of physicians, degree of geographic isolation and health care budget) were selected for the study and randomized to intervention or control. The intervention consisted of usual care, services of the Canadian Diabetes Association (CDA) Traveling Diabetes Resource Program (TDRP), academic detailing of primary care physicians, in-services for allied health professionals, referral services and public lectures to the community. The control group received the usual care and services of the CDA TDRP. Study participants were followed for 6 months. The primary study endpoint was a 10% reduction in HbA1c, systolic or diastolic blood pressure, or total cholesterol level. HRQL was a secondary study outcome, measured at baseline and 6 months. Ethical approval for the larger study was obtained through the University of Alberta Health Research Ethics Board Panel A.

In order to be included in the study, subjects had to have type 2 diabetes, live within the control or intervention region, consent to baseline measurements, be sufficiently literate in English to answer surveys and be willing to participate in follow-up visits. Subjects were excluded if they were discovered not to have type 2 diabetes or if they had a life expectancy of less than 6 months. Of the 394 subjects originally enrolled in the study, 372 completed baseline HRQL questionnaires. All HRQL measures were self-administered, self-completed and submitted via mail or at the time of a study visit. The HUI2 and HUI3 were administered as a single 15-item questionnaire from which scores for both instruments can be derived. This version of the HUI2 and HUI3 uses a 4-week recall period. The HUI2 and HUI3 are proprietary and require a fee and permission for use from Health Utilities Incorporated.(24)

3.2.2 Measures

In the HUI2 system (Appendix B), HRQL is characterized by six attributes: sensation (vision, hearing, speech), mobility, emotion, cognition, self-care, and pain/discomfort.(21) Overall utility scores on the HUI2 can range from -0.03 to 1.0, with -0.03 representing the utility of the worst possible HUI2 health state, 0.0 representing dead and 1.0 representing perfect health.(21) The HUI3 defines HRQL on eight attributes including vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain/discomfort (Appendix C).(20) Overall scores on the HUI3 can range from -0.36 to 1.0, with -0.36 representing the utility of the worst possible HUI3 health state (all attributes at the lowest level), 0.0 representing dead and 1.0 representing perfect health.(20)

For the single attributes of both instruments, scores can range from 0.0 to 1.0, with a score of 0.0 representing the lowest level of functioning on an attribute (for instance, "unable to control or move arms and legs" on the HUI2 mobility attribute) and a score of 1.0 representing full functional capacity on an attribute. For both instruments, differences of greater than 0.03 on the overall scores and 0.05 or greater on the single attributes are considered to be clinically important.(25)

Multiplicative utility functions are used to determine utility scores for the HUI2 and HUI3.(20;21) The respective scoring functions have differences in the weighting of attributes and have substantially different lowest possible scores. The difference in lowest possible score is, in part, the result of the strategies used to assess preferences for states worse than dead for the two measures.(20;21) The utility of states worse than dead was assessed using the standard gamble approach and visual analog scale for the HUI3, but was assessed using only a visual analog scale for the HUI2. The standard gamble approach involves decision making under uncertainty and is consistent with Von Neumann-Morgenstern utility theory(22); thus, overall HUI3 scores may better reflect community preferences for states worse than dead. Further, the HUI3 more precisely discriminates among higher levels of impairment, due to the larger number of levels for several attributes.(20)

3.2.2.1 The HUI2 and HUI3 in Diabetes

Both the HUI2 and HUI3 contain attributes that would likely be affected by diabetes and diabetic complications. Diabetic complications such as amputation and peripheral neuropathy would presumably affect the mobility and self-care attributes of the HUI2 and the ambulation and dexterity attributes of the HUI3. Neuropathy and myopathy would likely affect the pain and discomfort attribute of the HUI2 and HUI3 and the dexterity attribute of the HUI3. Finally, retinopathy would likely affect the vision attribute of the HUI3 and the sensation attribute of the HUI2.

It is important to note, however, that differences in the content of overlapping attributes of the HUI2 and HUI3 may affect performance of either instrument in type 2 diabetes Pain and emotion are likely to be affected by severity of diabetes. The specific content and number of levels of those attributes differ between the two measures. The pain and discomfort attribute of the HUI2 is focused on alleviation of pain through medication, whereas the pain attribute of the HUI3 is more focused on the degree of disruption of activities. The emotion attribute of the HUI2 focuses on worry and anxiety, while the emotion attribute of the HUI3 specifically assesses happiness versus depression. It is not clear which content would better reflect the pain and emotional deficits associated with diabetes. Overall, though, the HUI3 is less subject to floor effects than is the HUI2.

3.2.3 Data Analysis

Tests of statistical significance analysis of variance ([ANOVA] and t-tests) were used to determine if differences existed in average single attribute and overall HUI2 and HUI3 utility scores of groups with presumed differences in disease severity or stability of control. We hypothesized that groups with more advanced or severe diabetes and unstable control would have relatively lower overall HUI2 and HUI3 scores and lower relevant single attribute utility scores.

We defined disease severity or advancement in terms of treatment intensity of diabetes. Treatment of diabetes was used as an indicator because the CDA recommended a step-wise approach to the management of type 2 diabetes, starting with diet alone, then oral hypoglycemics agents and, finally, insulin therapy in the treatment guidelines that were in place during the study.(26) Thus, individuals treated with insulin were presumed to have the most advanced disease, while individuals managed using diet alone were presumed to have the least advanced disease. In past research, greater intensity of treatment has been associated with poorer HRQL in type 2 diabetes.(7-9;27)

We collected data on absenteeism from work due to diabetes, emergency room visits for diabetes and glycosylated hemoglobin (HbA1c) to assess stability of disease control.(5;26;27) For those measures, individuals were categorized as having taken no days off versus one or more days off of work due to diabetes (for individuals who indicated that they were presently employed) and having had no emergency room visits versus one or more emergency room visits. In terms of glycemic control, we categorized individuals according to targets for diabetes management from the clinical practice guidelines for management of diabetes in Canada that were in place at the time of the study. A HbA1c of less than 0.070 was considered the optimal target goal, 0.071 to 0.084 was indicative of less than optimal control possibly warranting action, and levels greater than 0.084 indicated inadequate control and that action was needed.(26)

To compare the ability of each instrument to assess greater levels of impairment, the proportion of subjects rated as moderately to severely impaired on attributes likely to be affected by diabetes was determined.(24) For the HUI2, those attributes included sensation, mobility, emotion, self-care, and pain. Relevant HUI3 attributes included vision, ambulation, dexterity, emotion, and pain. For all attributes, level 1 represented no impairment, level 2 represented mild impairment and levels 3 or higher indicated moderate to severe impairment.

To allow us to determine the percent of difference in overall scores attributable to differences in scale ranges rather than instrument content, we employed methods used by Neumann and colleagues, who compared HUI2 and HUI3 scores in Alzheimer's Disease.(28) Each measure was re-scaled on a 0.0 to 1.0 metric, such that 0.0 became the worst possible health state for each scale, while 1.0 remained perfect health. To further explore the effects of states worse than dead, HUI2 and HUI3 scores were compared for individuals with negative HUI3 utility scores.

3.2.3.1 Statistical Significance Testing

For comparisons between two groups, we employed t-tests; comparisons between three groups were tested using ANOVA with Scheffé post-hoc tests. When the distribution of the dependent variables was not normal, we also used nonparametric tests of significance; in all cases those analyses yielded the same conclusions, so we report only the parametric results. Differences in the proportion of individuals rated as moderately to severely impaired on overlapping HUI2 and HUI3 attributes were assessed using McNemar tests.

To determine the percent difference in overall scores due to scoring functions, we determined the difference in overall HUI2 and HUI3 scores before and after rescaling. The difference between HUI2 and HUI3 scores after re-scaling was then subtracted from the difference between HUI2 and HUI3 scores before re-scaling and the result was then divided by the difference between HUI2 and HUI3 scores before re-scaling and converted to a percent (see Table 3-5 footnote). For individuals with negative HUI3 scores, overall HUI2 and HUI3 scores and re-scaled scores were compared using the Wilcoxon signed rank test.

3.3.0 Results

The majority of the sample was female, married and had not completed high school (Table 3-1). The median duration of diabetes was 5.0 years (interquartile range [IQR]: 2.0 – 12.0 years). The most common treatment of diabetes was oral medication, although a substantial proportion of the sample (27 %) was treated with insulin.

As anticipated, overall HUI2 scores were higher than overall HUI3 scores (median [IQR] = 0.82 [0.72 - 0.92] versus 0.70 [0.49 – 0.91]), although the shape of the distribution of scores was similar (Figure 3-1 and Figure 3-2). The percentage of the study sample with missing HRQL data ranged from a low of 1% for the self-care attribute of the HUI2 to a high of 16% for the HUI2 overall score. Subjects missing overall HUI2 and HUI3 scores were statistically significantly older, had lower incomes and were more likely to use insulin and/or oral medications than to be managed on diet alone than subjects with complete data.

3.3.1 Categorization of Level of Impairment

The vast majority of subjects had impairment on the vision and sensation attributes of the HUI3 and HUI2, respectively (Table 3-2 and Table 3-3). Further, a large proportion, approximately two-thirds of subjects, reported some degree of pain. Emotional problems were also highly prevalent in this sample; almost one-half of subjects experienced some degree of impairment on the emotion attribute on both the HUI2 and HUI3. The pain and emotion attributes of the HUI3 clearly categorized a larger proportion of individuals as moderately to severely impaired relative to the HUI2 ($p < 0.001$ for each paired comparison) (Figure 3-3). More individuals were categorized as moderately to severely impaired on the HUI3 dexterity attribute than the HUI2 self-care attribute ($p=0.003$). The sensation attribute of the HUI2 categorized more individuals as moderately to severely impaired than the HUI3 vision attribute ($p < 0.001$). Classification of subjects with respect to severity on the HUI2 mobility and HUI3 ambulation attributes was identical.

3.3.2 HUI2 and HUI3 Single Attribute Scores

Differences in the HUI2 sensation attribute failed to reach the guideline for clinical importance for any of the grouping variables, while clinically important differences on the HUI3 vision attribute were noted between individuals whose diabetes was managed by diet alone compared with insulin (a difference of 0.07 units) and individuals with the lowest HbA1c levels compared with the highest (a difference of 0.06 units) (Tables 3-4 and 3-5).

Patterns in differences for the mobility and ambulation attributes were virtually identical across all comparisons, with differences in scores by treatment regimen on both attributes reaching statistical significance and clinical importance (Table 3- 4). Neither the dexterity nor the self-care attribute detected clinically meaningful differences for any comparison (Table 3-4 and Table 3-5).

Statistically significant or clinically important differences in the emotion attributes of both the HUI2 and HUI3 were detected for all comparisons between groups (Table 3-4 and 3-5). The magnitude of the difference in emotion between groups according to emergency room visits was larger for the HUI2 than the HUI3 (Table 3-5). For the pain attributes, the difference in scores according to level of absenteeism from work, number of emergency room visits, HbA1c level and treatment regimen were much larger for the HUI3 than the HUI2 (Table 3-4 and 3-5). These differences were clinically important for all comparisons using the HUI3 pain attribute, but only for the comparisons according to HbA1c level and absenteeism from work for the pain attribute of the HUI2.

3.3.3 Overall HUI2 and HUI3 Scores

Overall HUI2 and HUI3 scores both detected statistically significant differences according to stage of disease (Table 3-4) and clinically important differences according to stability of glycemic control (Table 3-5). The differences exceeded 0.03 for comparisons involving treatment intensity using the HUI3 and, thus, would be considered clinically important. The difference in overall HUI2 scores between individuals managed by diet alone compared with those taking oral agents (0.02) were not quite clinically important.

Relative to HUI2 scores, much larger differences in overall HUI3 scores were seen for comparisons according to glycemic control (Table 3-5). Although all differences were clinically important, the magnitude of the difference in overall HUI3 scores was three times the difference in HUI2 scores for emergency room visit status (0.15 versus 0.05) and almost five times the magnitude for absenteeism from work status (0.19 versus 0.04). The difference in overall HUI3 scores according to emergency room use was the only indicator of unstable control to reach statistical significance ($p < 0.05$).

Fourteen individuals had negative HUI3 scores (indicating their health states were valued by the community as being worse than dead), but no subject had a negative HUI2 score. The mean difference between HUI2 and HUI3 scores for the subjects with negative HUI3 scores was statistically significant (mean difference = 0.41, $p < 0.001$). Interestingly, after rescaling, two individuals' overall HUI2 scores were actually lower than their HUI3 scores; however, the trend of overall HUI2 scores exceeding overall HUI3 scores persisted (mean difference = 0.14, $p = 0.009$). After converting overall HUI2 and HUI3 scores to the same metric, the difference in HUI2 and HUI3 scores across groups became much smaller (Table 3-6). The relative proportion of difference between overall HUI2 and HUI3 scores that was attributable to scaling alone ranged from 31% for individuals with a HbA1c level < 0.070 to 75% for individuals who did not require any days off work. In the entire sample, the average difference between HUI2 and HUI3 scores decreased from 0.14 to 0.04 after rescaling.

3.4.0 Discussion

Our results demonstrate that the HRQL deficits and level of impairment associated with type 2 diabetes differ substantially when measured by the HUI3 versus the HUI2. Differences in overall HUI2 and HUI3 scores could be attributable to differences in scales, scoring functions, the number of levels for each attribute, the specific attributes included in the measures and the difference in content of overlapping attributes measured by the instruments. From this analysis, it was apparent that scale differences played an important role, as did the content of overlapping attributes.

The HUI3 revealed greater overall HRQL deficits than the HUI2. These differences persisted after re-scaling each measure on a common 0 to 1 scale, although the magnitude decreased. The percent difference in overall HUI2 and HUI3 scores attributable to the scale difference ranged from 31% to 75%. The percent of difference in overall HUI2 and HUI3 scores attributable to scale ranges was similar to that obtained in patients with Alzheimer's disease (28), where differences ranged from 52% to 76%. Differences reported in the literature between HUI3 and HUI2 scores in conditions with substantial morbidity burden are large. In Alzheimer's disease, average HUI2 scores were 0.53, compared with 0.22 for HUI3 scores.(28) The differences in HUI3 versus HUI2 scores in our study were closer to the differences found in patients with hemophilia(29) (average HUI2 scores were 0.81 compared with 0.71 for HUI3 scores) and in patients with total hip arthroplasty (0.62 versus 0.52, respectively).(30)

No subject was classified in a health state worse than dead according to the HUI2, while 14 subjects were considered in health states worse than dead according to the HUI3. This finding could re-affirm the concern that the HUI2 did not give enough weight to communities' preferences for states worse than dead.(21) Examination of the vectors for these 14 individuals showed substantial emotional, pain, vision and hearing deficits, with six individuals indicating that they were so unhappy that life was not worthwhile. It appeared that the valuation of their states had face validity, but it is important to note that scores reflect community preferences, not the individual's preferences. Community preferences often tend to be lower than those of individuals experiencing a particular health state.(31;32) While it is possible that the differences in overall HUI scores arose from excessive weight on deficits in the HUI3, we tend to favor the alternative position that overall HUI3 scores may better capture the overall burden of type 2 diabetes.

Differences in the content of overlapping HUI2 and HUI3 single attributes also appeared to make an important contribution to differences in overall HUI2 and HUI3 scores. Generally, scores on the pain attribute were lower on the HUI3 than the HUI2 and the magnitudes of the differences were substantially larger for comparisons using the HUI3. Consistent with this finding, a larger percent of individuals were classified as having moderate to severe pain according to the HUI3 pain attribute than the HUI2 pain attribute (42% versus 24 %), indicating that the pain attribute of the HUI3 perhaps captured more of the type of pain associated with the complications of diabetes.

Both types of emotion assessed by the HUI2 and HUI3 appeared to be important in diabetes. Interestingly, a greater emotional burden was associated with recent emergency room visits on the HUI2 emotion attribute than the HUI3 emotion attribute, but overall, more individuals experienced moderate to severe impairment on the HUI3 (21%) emotion attribute (perceived happiness) than the HUI2 (8%) emotion attribute (anxiety and worry). The greater sensitivity of the HUI2 to the burden associated with emergency room visits may result from the HUI2's focus on worry and anxiety as opposed to the HUI3's focus on happiness versus depression.

The sensation attribute of the HUI2 identified more individuals as having moderate to severe impairments, likely attributable to the fact that the HUI2 sensation attribute encompasses three senses - vision, hearing and speech. Hearing and speech are less germane to type 2 diabetes than vision, so the HUI3 vision attribute may be more appropriate here than the HUI2 sensation attribute. Further, the vision attribute of the HUI3 is likely to be more precise as it separates individuals into six levels while the sensation attribute of the HUI2 has only four levels.

Although our results support the ability of the HUI2 and HUI3 to capture HRQL deficits in type 2 diabetes, a number of study limitations should be recognized. First, the number of individuals for which HRQL data was missing was, in some cases, substantial, and statistically significant differences between individuals with complete and missing data for HUI2 and HUI3 were found. Individuals missing HRQL data were older and of lower socio-economic status. We do not think, however, that such differences would affect the internal validity of the study results or the construct validity of the measures.

Furthermore, data on treatment for diabetes, emergency room visits and absenteeism from work were based on self-report; nevertheless, a high level of agreement (kappa=0.93) was found when self-reported data were compared with data obtained through a formal medication history taken from our participants by research coordinators.(33) Also, we did not collect information on specific complications associated with HRQL in diabetes.(34) Instead, we used treatment as an indirect measure of disease severity, with the assumption that more prolonged and advanced diabetes would be associated with more complications.

3.5.0 Conclusions

The HUI3 appeared to be more sensitive to the HRQL deficits associated with disease severity or advancement and poor diabetic control and, thus, may be preferred over the HUI2. In this sample, it appears that the HUI2 did not offer any specific advantage over the HUI3, other than greater sensitivity to the emotional deficits associated with recent visits to an emergency room. The greater range of possible scores on the HUI3, its ability to assess the utility of states worse than dead, and its superiority in discriminating moderate to severe impairment from mild or no impairment might favor the use of the HUI3 over the HUI2 in assessing HRQL in diabetes. Using the HUI2 produces higher utility scores than does the HUI3 for individuals with moderate to severe impairment and, thus, may underestimate the true HRQL deficits associated with type 2 diabetes. Relative to the HUI3, the HUI2 might also understate gains associated with effective interventions.

It may be worth assessing the relative performance of the HUI2 and HUI3 in a larger sample of individuals with type 2 diabetes and in individuals with type 1 diabetes before generalizing our findings to the ambulatory population of individuals with diabetes. Future research should explore the relationships between these HRQL measures and diabetic complications directly, the responsiveness of these two measures to detect within-person change over time, potential differences in results in cost-utility studies of type 2 diabetes, and the difference between the two measures in other diseases.

Table 3-1: Demographic, Clinical and HRQL Characteristics (n=372)

Age (years) - Mean (SD)	62.3 (12.5)
Sex, Males (%)	41.6
Annual Income (CDN $) (%)	
less than $5,000	8.1
$5,000 to $19,999	31.0
$20,000 to 39,999	22.8
greater than $40,000	21.6
Currently married (%)	57.6
English as first language (%)	68.3
Graduated high school (%)	30.5
Currently working (%)	26.9
Duration of diabetes (years) – Median (Interquartile Range)	5.0 (2.0 – 12.00)
Glycosylated hemoglobin Level (%) – Median (Interquartile Range)	7.0 (6.2 – 8.1)
Body mass index (kg/m^2)- Mean (SD)	32.9 (6.7)
Total cholesterol level (mmol/L) - Mean (SD)	4.96 (1.0)
Systolic blood pressure (mmHg) - Mean (SD)	131 (18.6)
Diastolic blood pressure (mmHg) - Mean (SD)	76 (11.5)
Treatment of diabetes (%)	
Diet only	17.5
Oral hypoglycemic agent	48.2
Insulin alone or insulin plus an oral hypoglycemic agent	27.2
Missing	7.1
One or more emergency room visits for diabetes in past 6 months - (%)	5.3
One or more hospitalizations due to diabetes in past 6 months - (%)	7.1
One or more days off of work due to diabetes in past 6 months - (%)	6.6

Table 3-2: Distribution of Levels on HUI2 Attributes (% of Subjects) and Single-Attribute Utility Scores

	Sensation		Mobility		Emotion		Cognition		Self-Care		Pain	
	Utility	%	Utility	%	Utility	%	Utility	%	Utility	%	Utility	%
Level 1	1.0	8.6	1.0	64.2	1.0	47.2	1.0	48.5	1.0	87.8	1.0	25.4
Level 2	0.87	52.8	0.92	16.8	0.86	37.8	0.85	40.6	0.85	3.8	0.95	43.7
Level 3	0.65	19.5	0.61	8.9	0.60	5.1	0.55	2.5	0.55	0.80	0.75	13.7
Level 4	0.0	3.0	0.34	0.80	0.37	1.0	0.0	0.0	0.0	0.50	0.42	5.6
Level 5	-	-	0.0	0.0	0.0	1.0	-	-	-	-	0.0	2.8
Missing	-	16.0	-	9.4	-	7.9	-	8.4	-	7.1	-	8.9

HUI2 – Health Utilities Index Mark 2

Table 3-3: Distribution of Levels on HUI3 Attributes (% of Subjects) and Single-Attribute Utility Scores

	Vision		Hearing		Speech		Ambulation		Dexterity		Emotion		Cognition		Pain	
	Utility	%	Utility	%	Utility	%	Utility	%	Utility	%	Utility	%	Utility	%	Utility	%
Level 1	1.0	11.2	1.0	72.6	1.0	81.2	1.0	64.2	1.0	77.2	1.0	42.9	1.0	48.5	1.0	26.1
Level 2	0.95	67.5	0.86	2.0	0.82	3.3	0.83	16.8	0.88	10.7	0.91	30.7	0.86	4.3	0.92	27.9
Level 3	0.73	2.3	0.71	2.3	0.67	4.6	0.67	7.1	0.73	1.5	0.73	13.5	0.92	20.6	0.77	22.8
Level 4	0.59	4.3	0.48	9.1	0.41	0.80	0.36	1.8	0.45	2.5	0.33	3.6	0.70	15.2	0.48	10.4
Level 5	0.38	4.1	0.32	0.80	0.0	0.0	0.16	0.8	0.20	0.8	0.0	2.0	0.32	3.0	0.0	5.1
Level 6	0.0	0.3	0.0	2.8	-	-	0.0	0.0	0.0	0.0	-	-	0.0	0.0	-	-
Missing		10.4		10.4		10.2		9.4		7.4		7.4		8.4		7.6

HUI3 – Health Utilities Index Mark 3

Table 3-4: HUI2 and HUI3 Overall and Single Attribute Scores by Treatment of Diabetes

HUI Score	Treatment of Diabetes		
	Diet Mean (SD)	Oral Agents Mean (SD)	Insulin +/- Oral Agent Mean (SD)
HUI2			
Overall	0.80 (0.18) *	0.78 (0.16)	0.74 (0.20)
Sensation	0.80 (0.19)	0.80 (0.20)	0.81 (0.17)
Mobility	0.96 (0.09) †	0.95 (0.12) ‡	0.91 (0.16)
Emotion	0.94 (0.09) §	0.91 (0.14)	0.86 (0.19) †
Cognition	0.94 (0.08)	0.93 (0.08)	0.92 (0.08)
Self-Care	0.99 (0.03)	0.99 (0.04) ‡	0.96 (0.15)
Pain	0.87 (0.22)	0.89 (0.19)	0.85 (0.25)
HUI3			
Overall	0.69 (0.30) *	0.64 (0.29)	0.59 (0.30)
Vision	0.94 (0.08)	0.91 (0.14)	0.87 (0.19)
Hearing	0.90 (0.25)	0.88 (0.25) ‡	0.94 (0.20)
Speech	0.98 (0.09)	0.97 (0.10)	0.98 (0.08)
Ambulation	0.95 (0.13) †	0.93 (0.14) ‡	0.89 (0.18)
Dexterity	0.97 (0.12) †	0.97 (0.09) ‡	0.93 (0.17)
Emotion	0.93 (0.12) †	0.89 (0.20)	0.85 (0.23)
Cognition	0.91 (0.14)	0.90 (0.16)	0.90 (0.15)
Pain	0.80 (0.28)	0.83 (0.20)	0.75 (0.31)

HUI2 – Health Utilities Index Mark 2; HUI3 – Health Utilities Index Mark 3

* $p < 0.05$ for comparison between diet and insulin +/- oral agent groups

† $p < 0.01$ for comparison between diet and insulin +/- oral agent groups

‡ $p < 0.05$ for comparison between oral agent and insulin +/- oral agent group

§ $p < 0.05$ for comparison between diet and oral agent groups

Table 3-5: HUI2 and HUI3 Overall and Single Attribute Scores by Emergency Room Visits, Days off Work and HbA1c Level

HUI Score	**ER Visits** Mean (SD)		**Days off Work** Mean (SD)		**HbA1c Level** Mean (SD)		
	No Visits	One or More Visits	No Days Off Work	One or More Days off Work	< 0.070	0.070 – 0.084	> 0.085
HUI2							
Overall	0.78 (0.18)	0.73 (0.16)	0.85 (0.12)	0.81(0.19)	0.78 (0.17)	0.79 (0.15)	0.75 (0.22)
Sensation	0.80 (0.19)	0.84 (0.14)	0.85 (0.13)	0.85 (0.16)	0.80 (0.19)	0.80 (0.19)	0.81 (0.19)
Mobility	0.94 (0.13)	0.90 (0.16)	0.99 (0.03)	0.99 (0.03)	0.94 (0.14)	0.95 (0.11)	0.94 (0.13)
Emotion	0.91 (0.14)*	0.80 (0.22)	0.93 (0.09)	0.87 (0.12)	0.92 (0.13) §	0.91 (0.13)	0.86 (0.20)
Cognition	0.93 (0.08)	0.91 (0.07)	0.95 (0.07)	0.97 (0.06)	0.93 (0.08)	0.93 (0.08)	0.93 (0.09)
Self-Care	0.98 (0.09)	0.98 (0.05)	1.00 (0.02) ‡	0.98 (0.05)	0.99 (0.09)	0.99 (0.06)	0.98 (0.13)
Pain	0.87 (0.22)	0.90 (0.15)	0.93 (0.16)	0.88 (0.19)	0.87 (0.20)	0.89 (0.19)	0.84 (0.27)
HUI3							
Overall	0.65 (0.30) †	0.50 (0.24)	0.77 (0.23)	0.58 (0.35)	0.65 (0.29)	0.66 (0.27)	0.60 (0.34)
Vision	0.90 (0.15)	0.89 (0.18)	0.93 (0.10) ‡	0.97 (0.03)	0.92 (0.14) §	0.92 (0.11) **	0.86 (0.20)
Hearing	0.90 (0.24)	0.94 (0.17)	0.95 (0.16) ‡	0.83 (0.26)	0.89 (0.24)	0.88 (0.25)	0.93 (0.21)
Speech	0.97 (0.10)	0.99 (0.04)	0.99 (0.04)	0.96 (0.11)	0.97 (0.10)	0.96 (0.10)	0.98 (0.09)
Ambulation	0.93 (0.15)	0.89 (0.14)	0.98 (0.05)	0.98 (0.06)	0.92 (0.16)	0.92 (0.14)	0.92 (0.14)
Dexterity	0.96 (0.13)	0.99 (0.03)	0.99 (0.04)	0.97 (0.05)	0.96 (0.12)	0.96 (0.13)	0.95 (0.14)
Emotion	0.89 (0. 20) †	0.82 (0.21)	0.93 (0.11) ‡	0.85 (0.12)	0.89 (0.18)	0.90 (0.19)	0.84 (0.25)
Cognition	0.91 (0.16)	0.85 (0.18)	0.94 (0.13)	0.96 (0.10)	0.90 (0.16)	0.91 (0.13)	0.90 (0.16)
Pain	0.81 (0.25)	0.70 (0.32)	0.87 (0.19) ‡	0.63 (0.38)	0.82 (0.23)	0.83 (0.21)	0.74 (0.33)

Note: HUI2 – Health Utilities Index Mark 2; HUI3 – Health Utilities Index Mark 3, ER – Emergency Room

* $p \leq 0.001$ for comparison between no ER visits and one or more ER visits groups

† $p < 0.05$ for comparison between no ER visits and one or more ER visits groups

‡ $p < 0.05$ for comparison between no days off work and one or more days off work groups

§ $p < 0.05$ for comparison between < 0.070 and > 0.085 groups

** $p < 0.05$ for comparison between 0.070 – 0.084 and > 0.085 groups

Table 3-6: Percent of Difference in Overall HUI2 and HUI3 Scores Attributable to Differences in Scale Range

	Overall HUI Scores Mean (SD)		Re-Scaled Overall HUI Scores Mean (SD)		Percent of Difference Attributable to Scale*
	HUI2	HUI3	HUI2(R)	HUI3(R)	
Treatment					
Diet	0.80 (0.18)	0.69 (0.30)	0.81 (0.17)	0.77 (0.22)	63.4
Oral Agents	0.78 (0.16)	0.64 (0.29)	0.79 (0.16)	0.74 (0.21)	61.5
Insulin	0.74 (0.20)	0.59 (0.30)	0.75 (0.19)	0.70 (0.22)	66.7
ER Visits					
None	0.78 (0.18)	0.65 (0.30)	0.78 (0.17)	0.74 (0.22)	69.2
One or more	0.73 (0.16)	0.50 (0.24)	0.74 (0.14)	0.64 (0.18)	56.5
Days off Work					
None	0.85 (0.12)	0.77 (0.23)	0.85 (0.12)	0.83 (0.17)	75.0
One or more	0.81 (0.19)	0.58 (0.35)	0.81 (0.18)	0.69 (0.26)	47.8
HbA1c					
< 0.070	0.78 (0.17)	0.65 (0.29)	0.83 (0.09)	0.74 (0.19)	30.8
0.070 – 0.084	0.79 (0.15)	0.66 (0.27)	0.80 (0.15)	0.75 (0.20)	61.5
> 0.085	0.75 (0.22)	0.60 (0.34)	0.75 (0.21)	0.70 (0.25)	66.7

Note: HUI2 – Health Utilities Index Mark 2; HUI3 – Health Utilities Index Mark 3; HUI2 (R) – Health Utilities Index Mark 2 Re-scaled;
HUI3 (R) – Health Utilities Index Mark 3 Re-scaled
* $\frac{(A - B)}{A}$ x 100 where A = HUI2 – HUI3 and B = HUI2(R)– HUI3(R)

Figure 3-1: Distribution of HUI2 Scores

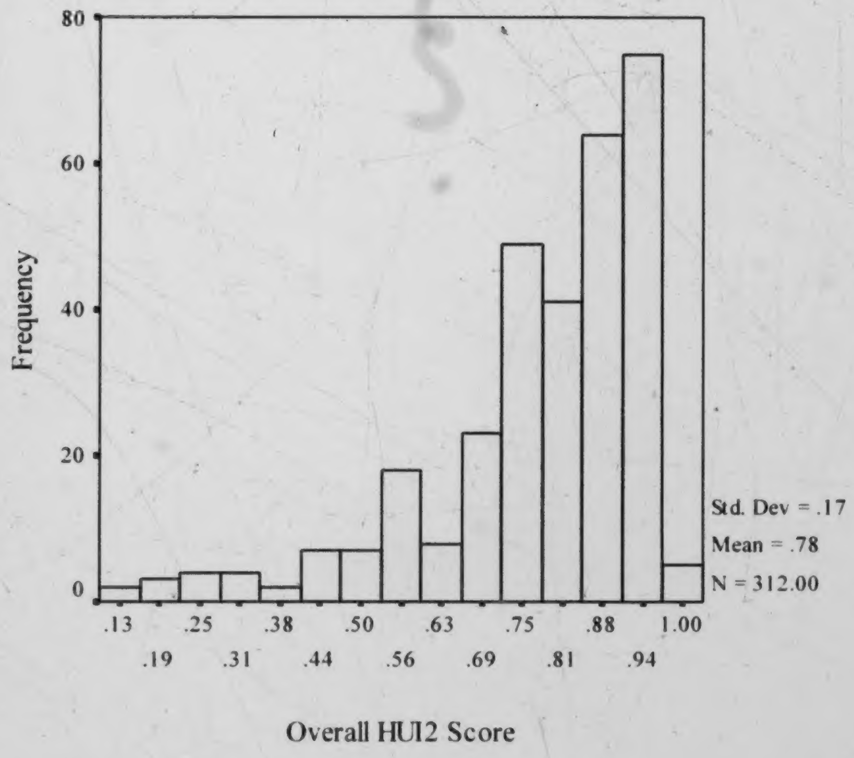


Figure 3-2: Distribution of Overall HUI3 Scores

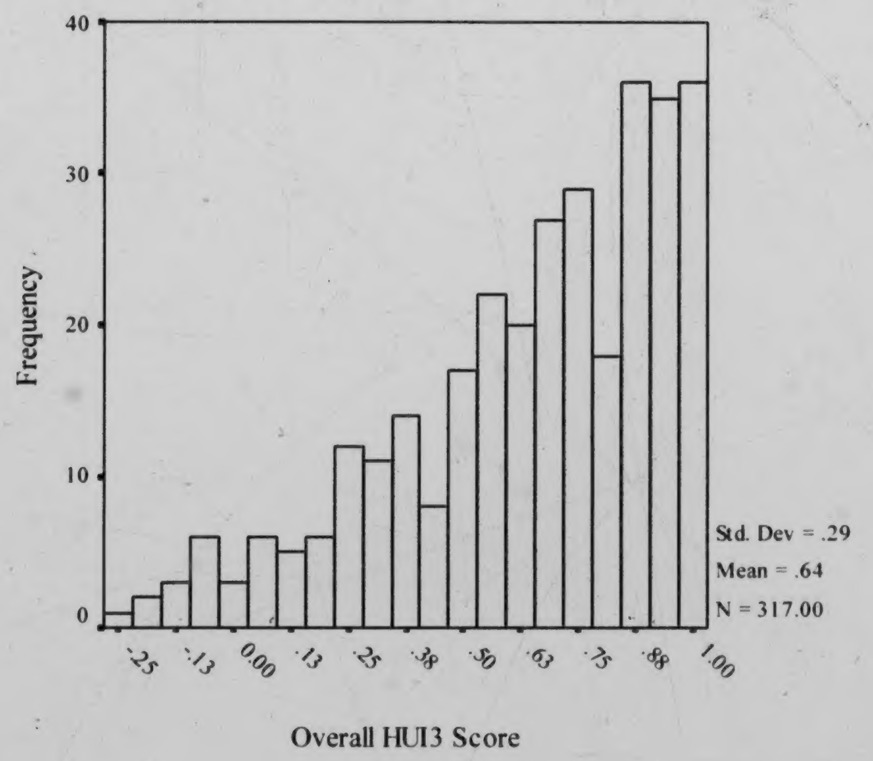
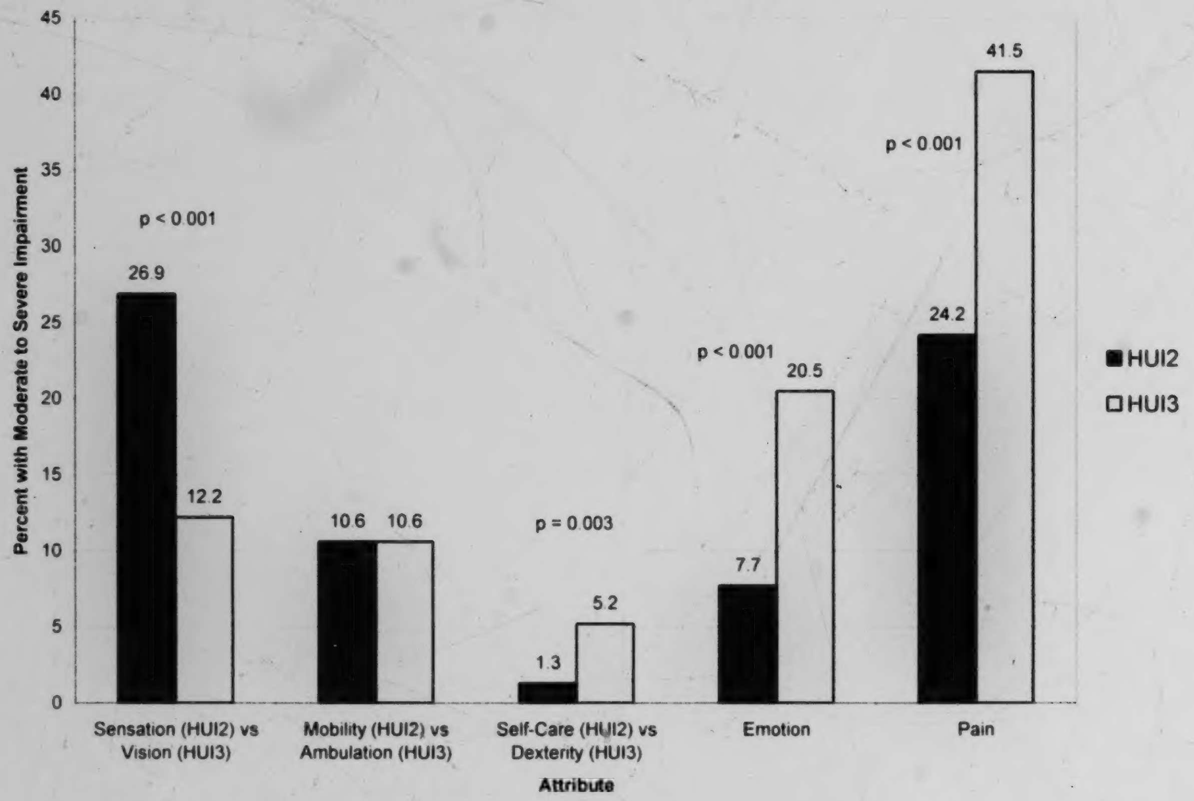


Figure 3-3: Subjects with Moderate to Severe Impairment on Overlapping Attributes



Note: Moderate to severe impairment includes levels 3 or higher on each attribute of the HUI2 (Health Utilities Index Mark 2) or the HUI3 (Health Utilities Index Mark 3).

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Chapter 4 - Construct Validity of the Health Utilities Index Mark 3 in Type 2 Diabetes: Evidence from a Nationally Representative Sample of Canadians with Type 2 Diabetes[3]

4.1.0 Introduction

Diabetes places a substantial burden on individuals with the disease. The burden arises from the condition itself, complications or comorbidities associated with the disease and its treatment.(1-7) The morbidity burden of diabetes can be associated with impairment on many dimensions of health-related quality of life (HRQL), both physical and mental.(1;8-12) Although the literature regarding HRQL assessment in people with diabetes is extensive, many questions about the most appropriate measures remain.(13)

Much of the HRQL research in diabetes has focused on the development and application of diabetes-specific instruments.(14;15) Specific HRQL measures bring into focus the impact on health and functioning arising directly from a condition or treatment and are intended to provide greater detail concerning outcomes associated with a condition.(16) In contrast, generic HRQL measures are intended to provide information on the general function and well-being. The more general content of generic measures may make them better suited for particular applications. In diabetes, for example, disease specific measures fail to capture the additional HRQL deficits associated with comorbidities,(3;5;17) which make an important contribution to the disease burden.

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[3] The research and analysis are based on data from Statistics Canada. The opinions expressed do not represent the views of Statistics Canada.

Generic measures can be classified into health status profiles and preference-based index measures.(16) Preference-based index measures are based upon decision theory and economics and reflect preferences for alternative health outcomes.(16) Multi-attribute utility measures are a category of preference-based index measure.(16) General recommendations for assessments of HRQL suggest the concurrent use of several categories of measures (i.e. specific measures, generic health profiles and preference-based index measures) to capture a broad scope of health status.(18) In diabetes, it has been suggested that a combination of disease-specific and generic HRQL measures may be useful in order to provide complementary information.(3;5;19) As there are a variety of HRQL measures available from each category, selecting which instrument to use requires the consideration of a number of important factors. The choice may depend on the purpose of the measurement, the attributes of health that are relevant to the target population, and the evidence of construct validity of the measure in the target population (i.e. whether the instrument measures the intended property or concept in that population).(20)

Previous application of multi-attribute utility measures in diabetes has been relatively limited; thus, evidence of their construct validity in diabetes is presently limited. Before multi-attribute utility measures are widely used in research or clinical applications in type 2 diabetes or health policy decisions are based upon data derived from their use, it is important that we can be reasonably confident in their performance in the disease. The Health Utilities Indexes (HUI) are a family of multi-attribute utility measures that have been shown to identify HRQL deficits associated with type 2 diabetes(21-23) and the burden associated with comorbidities in diabetes in the general population.(24) As well, there is additional evidence of the construct validity of the HUI3 for arthritis and stroke.(25) We previously assessed the construct validity of the HUI3 in type 2 diabetes in a relatively small sample of rural Albertans, but we were unable to assess the ability of HUI3 to detect differences between groups of individuals with and without specific comorbidities or complications.(21-23)

Therefore, the overall objective of this research was to provide further evidence of the construct validity of the HUI3 in type 2 diabetes by (1) assessing the ability of the overall HUI3 scores and diabetes relevant single attributes to detect clinically important differences between groups anticipated to differ in their level of HRQL (i.e. according to duration of diabetes, treatment intensity, and comorbidities) and (2) assessing the association between previous healthcare resource utilization (physician visits, emergency department use and hospitalization) and current overall HUI3 scores.

4.2.0 Research Design and Methods

4.2.1 Survey Design

The data source of this analysis was the Canadian Community Health Survey (CCHS) Cycle 1.1. The CCHS is a cross-sectional survey of individuals aged 12 years and older.(26) Data was collected on utilization of health services, determinants of health and health status on a two year cycle.(26) The survey excludes individuals living on crown or reserve land, in institutions, members of the Canadian Armed Forces and some remote areas of the country. Even with these exclusions, 98% of the Canadian population over 12 years of age is represented.(26)

The sample of the CCHS was selected from two different sampling frames. One frame used a multistage stratified cluster design (83% of the sample) and the other used random digit dialing (17%) to select the sample. Data for Cycle 1.1 were collected between September 2000 and November 2001. Overall, 41.4% of respondents used in these analyses had telephone interviews, 56.7% had in person interviews and 1.9% were interviewed using a combination of techniques. At the end of Cycle 1.1, the overall response rate was 84.7%.(27)

4.2.2 Sample

Our analyses included CCHS respondents self-identified as having a diagnosis of diabetes by a health practitioner. An algorithm was used to categorize individuals as having type 1 or type 2 diabetes (Figure 4-1). The criteria of being less than 30 years old at diagnosis and being placed on insulin immediately has been used previously to classify individuals as having type 1 diabetes.(28) The use of oral agents to manage diabetes has been used previously to classify individuals as having type 2 diabetes.(29;30) All analyses were restricted to individuals over the age of 18 (Figure 4-2). In the CCHS, 6361 (4.1%) respondents self-reported having a diagnosis of diabetes, 5637 of which were categorized as having type 2 diabetes, representing a weighted percentage of the population of 90.1%.

In the CCHS, Statistics Canada carried out imputation using the "nearest neighbour" method (i.e. hotdecking) to handle missing data for a pre-defined set of variables for proxy respondents only.(26) We did not employ additional imputation methods for variables where it was considered inappropriate by Statistics Canada or where imputation did not improve data quality.(27) Without additional imputation, 5134 (91.2%) of the respondents over the age of 18 with type 2 diabetes had complete data to be included in this analysis (Figure 4-2).

4.2.3 Health Utilities Index Mark 3 (HUI3)

HUI3 is a preference-based measure of HRQL that uses a multiplicative utility function to assign valuations to different health states.(31;32) Using the multi-attribute approach, health states are defined by a classification system that includes a set of dimensions or attributes of HRQL, with a number of different levels of functioning for each attribute. In the HUI3 system, eight attributes, including vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain, define health status. Each attribute has five or six levels, creating 972,000 unique HUI3 health states (Appendix C).(31)

The overall utility function for the HUI3 was derived from visual analogue scale and standard gamble techniques and responses from random samples from the general population in Hamilton, Ontario, Canada.(31) Overall scores on the HUI3 range from -0.36 to 1.0, with -0.36 representing the utility of the worst possible HUI3 health state, 0.0 representing dead and 1.0 representing perfect health.(31) Differences of greater than 0.03 for HUI3 overall scores are considered to be clinically important.(33) For the single attribute utilities, scores range from 0.0 to 1.0, with a score of 0.0 representing the lowest level of functioning on an attribute and a score of 1.0 representing full functional capacity on an attribute. A difference of 0.05 on a single attribute is considered to be clinically important.(33)

4.2.4 Comparison Groups

Respondents were anticipated to differ in HRQL based on duration of diabetes(23;34;35), treatment intensity(23;34-36) and presence of comorbidities (stroke, heart disease, depression and cataracts).(24;28;34;35;37-39) Of the approximately 25 chronic medical conditions reported in the CCHS, comorbidities were selected based on their relevance in diabetes and ability to test the performance of the single attributes of the HUI3. Stroke and heart disease were selected as they are common macrovascular complications(17;40-42) and are typically associated with significant HRQL deficits.(17;25;41;43;44) It was hypothesized that depression could be used to assess the performance of the emotion attribute since depression is associated with a significant additional HRQL burden in diabetes.(45) Further, depression is a relevant comorbidity to include since diabetes is associated with an approximately two-fold increased risk of depression.(10) As cataracts may be associated with diabetes(46;47), this comorbidity was used to assess the performance of the vision attribute since retinopathy was not assessed in the CCHS.

Diagnoses of heart disease, stroke and cataracts were based upon self-report. For depression, the Composite International Diagnostic Interview Short Form for Major Depression (CIDI-SFMD) was used to assess the probability of a major depressive disorder. A probability of 0.90 is considered consistent with a diagnosis of Major Depressive Disorder in accordance with the DSM-IV diagnostic criteria.(48) Respondents were categorized based upon the presence or absence of stroke, heart disease, cataracts and depression. Duration of diabetes was determined from the respondents' age and self-reported age of diagnosis of diabetes. Respondents were grouped according to whether they were above or below the median duration of diabetes (6.0 years). Insulin use was a marker of treatment intensity.

4.2.5 Utilization of Health Care Resources

Three markers were used to assess the association between healthcare resource utilization and HRQL: overnight hospitalizations, emergency room visits and physician visits. A hospitalization was defined as a self-reported overnight stay in a hospital, nursing home or convalescent home in the previous 12 months. Respondents were categorized as having no overnight hospital stays or one or more. An emergency room visit was defined as a last contact with a physician or nurse in the past 12 months in the hospital emergency room. Respondents were categorized as having used an emergency room or not. Physician visits were defined as the number of consultations with medical doctors over the previous 12 months and a median split (median = 5.0) was used to separate respondents into two groups. The median split was chosen in order to treat number of physician visits as dichotomous. Its positively skewed distribution would be otherwise problematic. Since the majority of respondents (95%) had one or more physician visit in the previous year, it was felt that the median spit would be preferable to a comparison of respondents who did and did not visit a physician.

4.2.6 Data Analysis

Analysis of covariance (ANCOVA) models were used to determine if clinically important and statistically significant differences on the overall HUI3 scores and diabetes relevant single attribute scores (i.e. vision, ambulation, dexterity, emotion, cognition and pain and discomfort) existed between known groups. All models were adjusted for age in the quadratic form ($b_1$age + $b_2$age^2), education (less than high school; high school; some post secondary, college or trade school; or university), marital status (yes or no), aboriginal status (yes or no), and number of medical conditions other than the four comorbidities. Age was operationalized in the quadratic form as a nonlinear relationship between age and HRQL has been previously found in the Canadian population.(24;49)

In this sample respondents with longer self-reported duration of diabetes were more likely to use insulin ($p < 0.001$) and were more likely to self-report having heart, stroke and cataracts ($p<0.001$ for each). Respondents who used insulin were also more likely to report having heart disease (1.69, 95% CI: 1.43, 2.00), stroke (2.43, 95% CI: 1.84, 3.19) and cataracts (1.63, 95% CI: 1.34, 1.97). Since duration of diabetes was associated with insulin use and comorbidities, these variables were included in the models assessing differences in HUI3 between respondents above and below the median duration of diabetes. Similarly, in the comparisons of HUI3 scores between respondents who did and did not use insulin, duration of diabetes and comorbidities were included. All comorbidities of interest were included in models in which differences in HRQL between known groups of respondents with and without each comorbidity were assessed. This was in order to control for the effects of multiple comorbidities on HRQL.

Logistic regression analyses were used to assess the association between overall HUI3 scores and physician visits (above or below the median), overnight hospitalization (yes or no) and last contact in the emergency department (yes or no) as dependent variables. In these analyses, overall HUI3 scores were grouped into three categories reflecting level of impairment: none/mild (0.89 to 1.00), moderate (0.70 to 0.88) and severe (less than 0.70).(50) The models were adjusted for age, education, marital status, aboriginal status, insulin use, and comorbidities.

The multistage stratified cluster design used in the CCHS created an unequal probability of being selected for inclusion into the survey. Unless accounted for, point estimates (e.g. of regression coefficients, means, etc.) would be biased and sample variance would be underestimated. Thus, normalized sampling weights were applied to the analysis in order to produce unbiased point estimates.(27) Normalized sampling weights do not adjust for clustering or stratification(27); thus, bootstrap variance estimates were used to estimate 95% confidence intervals and p-values. All analyses were carried out with SPSS version 12.0 (SPSS Inc. Chicago IL).

4.3.0 Results

The average age of respondents included in the analysis was 61.7 ± 13.4, with just over one-half of respondents being male (52.3%) and 68.2% being married (Table 4-1). The median duration of diabetes was 6.0 years (IQR: 2.0 to 13.0) and 15.6% of respondents used insulin. Heart disease and cataracts were the most commonly reported comorbidities, affecting 21.1% and 14.7% of respondents, respectively. The average overall HUI3 score was 0.76 ± 0.28 in this sample, suggesting moderate health impairment.(50) The average HUI3 score for the entire population was 0.88 ± 0.19.

Respondents who were excluded from the analyses due to missing data on covariates (n=363) (Figure 4-2) had significantly lower scores ($p<0.05$) on the ambulation (-0.04, 95% CI: -0.08, -0.01), emotion (-0.06, 95% CI: -0.09, -0.02), cognition (-0.08, 95% CI: -0.11, -0.04), and pain and discomfort attributes (-0.11, 95% CI: -0.16, -0.05) and on the overall HUI3 scores (-0.16, 95% CI: -0.21, -0.11). With the exception of the ambulation attribute, these differences were clinically important. Respondents who had complete data on covariates, but were missing data on the HUI3 (n=88) (Figure 4-2) differed from those respondents included in the analysis (n=5134) on a number of characteristics. Respondents who were missing data were less likely to complete secondary education (59.4% versus 43.5% with less than secondary education, $p < 0.05$), had poorer self-rated health (2.09 ±0.91 versus 2.72 ±1.05, $p <0.05$), and had poorer performance on other measures of physical functioning (data not shown).(51)

The difference in overall HUI3 scores between respondents above and below the median duration of diabetes was clinically important and statistically significant (-0.04, 95% CI: -0.05, -0.02). Respondents above the median duration of diabetes did not have clinically important deficits on any of the single attributes relative to those below the median, after controlling for demographic characteristics, insulin use and comorbidities.

The difference in overall HUI3 scores between insulin users and non-users was clinically important (-0.06. 95% CI: -0.09, -0.03) (Table 4-2). While differences between these groups were statistically significant for several single attributes (vision and ambulation), they were not clinically important. The exception was the pain attribute, where a large deficit was observed (-0.07, 95% CI: -0.11, -0.04) (Table 4-2).

All of the comorbidities of interest were associated with clinically important deficits on the overall HUI3, but the deficit associated with cataracts failed to reach statistical significance (Table 4-3). Differences in overall HUI3 scores between respondents with and without depression (-0.17, 95% CI: -0.22, -0.12) and stroke (-0.15, 95% CI: -0.21, -0.09) were extremely large in magnitude (Table 4-3). Heart disease, stroke and depression were all associated with clinically important deficits on the pain attribute. Stroke was the only comorbidity associated with clinically important deficits on the ambulation attribute (-0.12, 95% CI: -0.17, -0.07), whereas both stroke and depression were associated with deficits on the cognition attribute (Table 4-3). As anticipated, the difference in scores on the emotion attribute between respondents with and without depression was large (-0.14, 95% CI: -0.17, -0.10).

Impairment on overall HUI3 scores was also associated with health care utilization after adjusting for the covariates in the models (Table 4-4). Relative to respondents whose overall HUI3 scores indicated severe impairment, respondents with no or mild impairment (OR=0.59, 95% CI: 0.48, 0.74) or moderate impairment (OR=0.66, 95% CI: 0.51, 0.86) had a lower probability of exceeding the median number of physician visits (Table 4-4). The probability of having an overnight hospitalization in the previous year (OR=0.67, 95% CI: 0.51, 0.89) or last contact with a physician or nurse in the emergency room (OR=0.46, 95% CI: 0.24, 0.86) was significantly reduced for those respondents whose overall HUI3 scores indicated no or mild impairment relative to those with severe impairment. Comorbidities, duration of diabetes and insulin use were also associated with utilization of health care resources (Table 4-4).

4.4.0 Discussion

Type 2 diabetes is a chronic medical condition that can be associated with impairments on multiple dimensions of HRQL. A valid measure of HRQL in diabetes should differentiate between individuals expected to differ in their illness burden. As hypothesized, we observed respondents with greater disease burden (based upon duration of disease, treatment intensity, and comorbidities) had lower overall scores on the HUI3 and some deficits on the single attributes. The evidence generated from these analyses provides additional evidence of the cross-sectional construct validity of the HUI3 in type 2 diabetes at the population level. This increases our confidence that the HUI3 is an appropriate HRQL measure for future clinical, research and health policy applications.

A clinically important difference in overall HUI3 scores was found between respondents above and below the median duration of diabetes. In a sample of rural Albertans with type 2 diabetes, we used also used duration of diabetes, based on a median split (5.0 years) for known groups comparisons.(23) In that analysis, the difference between groups was 0.07. It is not surprising that the magnitude of the difference between groups in the two studies was somewhat different. In the previous study, it was not likely that the sample was representative of individuals with type 2 diabetes. As well, that difference was not adjusted for comorbidities, insulin use or demographic characteristics.(23) Regardless, both studies do suggest that individuals with diabetes of longer duration have worse overall HRQL than those of shorter duration.

Insulin use was associated with a deficit on the overall HUI3 score that was twice the clinically important difference (-0.06). We had previously surmised that the burden associated with insulin may be the result of confounding with disease duration, comorbidities or demographic characteristics such as age.(21-23) In this analysis, we adjusted for these factors and found that this relationship persisted, which suggests that the HUI3 does detect burden associated with insulin use. Alternately, insulin use could remain a marker for some further unexplained variance in HRQL such as microvascular complications. Unfortunately, we were limited to controlling for those comorbidities assessed in the CCHS, so complications such as peripheral vascular disease and nephropathy remained potential confounders.

The hypothesized relationships between overall HUI3 scores and comorbidities were consistently supported in these analyses. The overall HUI3 scores clearly distinguished between respondents with and without the comorbidities of interest, suggesting that comorbidities made an important contribution to the disease burden in type 2 diabetes in this sample. Other utility measures have been shown to discriminate between individuals with diabetes according to comorbidities or complications and have also suggested comorbidities were associated with significant HRQL deficits.(28;34-39;52;53) The ability of the overall HUI3 and other generic HRQL measures to demonstrate relationships between comorbidities and HRQL in people with diabetes is an advantage over diabetes-specific measures, which often fail to demonstrate this relationship.(3;5;17) It is important for a HRQL measure to capture comorbidity burden in diabetes since it is one of the three factors thought to contribute to the over burden in diabetes (in addition to the disease itself and its treatment). Thus, in addition to population health applications, the HUI3 could provide complementary information along with a disease-specific measure in individuals with type 2 diabetes in different research settings.

Evidence of construct validity of the HUI3 single attribute scores in these analyses was not as consistent as the evidence generated for the overall scores. Hypotheses for the pain attribute were most consistently supported. Clinically important differences between groups were detected according to insulin use, heart disease, depression, and stroke. For clinicians who treat individuals with type 2 diabetes, this may be of relevance as it appeared that pain was not adequately managed in respondents with comorbidities. The emotion attribute performed well in discriminating between respondents whose scores on the CIDI-SFMD did and did not suggest depression. The extremely large burden associated with depression emphasizes the need to screen for and manage comorbid depression in diabetes. Differences on the emotion attribute according to treatment regimen or duration were not statistically significant, after controlling for comorbidities and other covariates. Previously we had found that the difference on the emotion attribute between respondents on insulin and those controlled by diet alone was clinically important and had felt that the burden associated with insulin use contributed to these differences.(21) Comorbidities were not controlled for in the analysis. It is now apparent that after doing so, the strength of the association between treatment intensity and the emotion attribute was weakened.

The association between healthcare resource utilization and HRQL is an approach to assessing the construct validity of the HUI3 which we had not previously explored. Consistent with past research using health profiles or disease specific measures of HRQL,(54-60) we did find that respondents with higher overall HUI3 scores consumed fewer healthcare resources. As the majority of the evidence to support the use of the HUI3 in type 2 diabetes has been previously generated from known groups comparisons, we felt that it was important to generate evidence using a different approach. Our confidence in the HUI3's construct validity in type 2 diabetes would have been weakened if those individuals who had poor health status were not more likely to consume health care resources. Thus, the observed relationship with healthcare resource utilization successfully triangulated the results from the known groups comparisons.

Generating population level of evidence to support the use of the HUI3 was important given that the HUI3 has been incorporated into a number of Statistics Canada's Surveys, for example the CCHS, the National Population Health Survey and the General Social

Survey. These surveys are the basis for much research and tracking of health trends in Canada; thus, there is the potential for resource allocation decisions to be made from their data. It is important to society that health policy decisions based upon data derived from methodologically sound sources, for instance, that data are measured with valid instruments. The results of this study can increase confidence that data reflecting the burden of type 2 diabetes generated with the HUI3 at the population level will be suitable for resource allocation decisions.

From a research perspective, it was important to generate evidence of construct validity of the HUI3 in type 2 diabetes as it is sometimes questioned whether generic HRQL measures, regardless of whether they are preference-based index measures or generic health profiles, are appropriate to use in the disease. Consequently, when study outcomes are measured with a generic measure, it may be questioned whether disease burden in type 2 diabetes was truly reflected, given the broad nature of the health dimensions contained in the measure. Having previous evidence of construct validity, such as the evidence generated by this study, helps to clarify this question. From a research perspective, the results of this study are important in that the application of the HUI3 in type 2 diabetes was furthered beyond a clinical study population(22;23), to the population level. Given the wealth of data available from Canadian population health surveys and the potential for research in type 2 diabetes with these surveys, this population-based assessment of the construct validity of the HUI3 is useful methodological background work that can be drawn upon.

In carrying out these analyses a number of limitations became apparent. One issue with the analysis was the use of a previously unvalidated algorithm to distinguish between respondents with type 1 and type 2 diabetes. A number of the criteria in the algorithm have been used previously(28-30), but the algorithm as a whole has not. While this algorithm is based on the typical clinical presentation of type 2 diabetes, some individuals included in the analysis may have had type 1 diabetes. It is important to point out that for those respondents that could be classified (99%), the split between type 1 and type 2 diabetes was 10% and 90%, which is generally recognized as the distribution of type 1 and type 2 diabetes in Canada.(61) Thus, we were confident in the ability of the algorithm to accurately classify respondents as having type 1 or type 2 diabetes.

Another potential limitation was related to the accuracy of self-reported medical conditions and healthcare utilization. Although the questions regarding medical conditions specified that the condition have been diagnosed by a health professional, there remained potential for individuals to over- or under-report any medical condition. According to data collected from the National Diabetes Surveillance System (NDSS), the prevalence of diabetes in Canada is 5.1% in people aged 20 and over.(62) In the CCHS, 4.7% of respondents over the age of 20 self-reported having a diagnosis of diabetes; thus, it is likely that the self-reporting of diabetes was at least fairly accurate. Healthcare resource utilization data were based on self-report over the previous year. While the ability to recall whether a last contact with a physician or nurse was in an emergency room or whether an overnight hospitalization had occurred in the previous year may be less prone to recall bias, the accuracy of self-reporting the number of physician visits over a full year is questionable.

The CCHS sample is representative of 98% of the community dwelling population in Canada; however, the exclusion of individuals who live on reserve lands was somewhat problematic in that only 1.7% of the sample was Aboriginal. We still felt that it was important to adjust the analyses for this covariate, but the standard errors associated with this variable were large as a result of the small sample. Further, the degree to which this sample was representative of Aboriginals with diabetes in Canada was questionable as there have been systematic differences between Aboriginals who live on and off reserves.(63;64) Analyses were performed with and without this variable and we found that it made little difference; we opted to retain it in the analyses.

A number of respondents were missing data on covariates and the variables used to separate respondents into known groups. These respondents tended to have worse HRQL. We do believe it was important, however, to adjust the known groups for these covariates and did retain over 90% of respondents over the age of 18 with type 2 diabetes. Generalizability of these results to the respondents with missing data may be limited due to the observed differences between responders and nonresponders.

4.5.0 Conclusion

Despite these limitations, we feel that this study provided evidence of the construct validity of the HUI3 and did so in a large, representative sample of the majority of the

Canadian population. In these analyses we found that the overall HUI3, the pain and discomfort attribute, and the emotion attribute distinguished between respondents anticipated to differ in their level of HRQL when grouped according to the factors thought to impact HRQL in diabetes. As anticipated, level of impairment on the HUI3 was associated with utilization of health care resources. Confidence that the HUI3 is a suitable instrument for population-based health status evaluation in type 2 diabetes has been increased through the accumulation of evidence of construct validity of this measure.

Table 4-1: Demographic Characteristics of Respondents with Type 2 Diabetes

	N=5134
Age – Mean (SD)	61.69 (13.44)
Sex – (% Male)	52.3
Level of Education - %	
Less than secondary	43.5
Secondary graduation	16.6
Some post-secondary, college, trade school	28.2
University degree	11.2
Marital Status – (% Married)	68.2
Duration of Diabetes – Mean (SD)	9.41 (9.91)
Proxy Completion – (% Proxy)	5.0
Aboriginal Status – (% Yes)	1.7
Number of Medical Conditions[A]	
Mean (SD)	3.24 (1.88)
Has Cataracts (% Yes)	14.7
Suffers the Effects of Stroke (% Yes)	5.2
Has Heart Disease (% Yes)	21.1
Predicted Probability of Depression > 0.90 - %	7.2
Overnight Hospitalization (% Yes)	17.5
Last Contact with Physician or Nurse in ER (% Yes)	3.0
Number of Physician Visits in Previous 12 Months – Median (Interquartile Range)	5.00 (3.00-11.00)
Uses Insulin (% Yes)	15.6
Self-Rated Health	
Excellent	4.5
Very Good	18.3
Good	35.2
Fair	28.4
Poor	13.6
Overall HUI3 Score	0.76 (0.28)
Vision	0.94 (0.10)
Hearing	0.97 (0.11)
Speech	1.00 (0.04)
Ambulation	0.93 (0.20)
Dexterity	0.99 (0.07)
Emotion	0.95 (0.12)
Cognition	0.94 (0.14)
Pain and Discomfort	0.85 (0.30)

A Number of medical conditions other than stroke, heart disease, cataract or depression

Table 4-2: Adjusted[a] Mean (95% CI) Difference in Overall and Single Attribute Utility Scores According to Insulin Use

	Respondents who do not use Insulin	Impact of Insulin on HRQL: Mean (95% CI)[b] Difference[c]
Overall	0.61 (0.58, 0.64)	**-0.06 (-0.09, -0.03)***
Vision	0.92 (0.91, 0.94)	**-0.02 (-0.03, - 0.003)***
Hearing	0.96 (0.95, 0.97)	0.00 (-0.02, -0.02)
Speech	0.99 (0.99, 1.00)	0.00 (0.00, 0.01)
Ambulation	0.88 (0.86, 0.91)	**-0.04 (-0.07, -0.01)***
Dexterity	0.98 (0.97, 0.99)	**-0.01 (-0.02, -0.001)***
Emotion	0.89 (0.88, 0.91)	0.00 (-0.02, 0.01)
Cognition	0.87 (0.86, 0.89)	0.00 (-0.01, 0.02)
Pain	0.74 (0.71, 0.78)	**-0.07 (-0.11, -0.04)***

a Adjusted for Age, Sex, Education, Marital Status, Race, Depression, Stroke, Heart Disease, Cataracts, Number of Other Medical Conditions, and Duration of Diabetes

b 95% Confidence Interval based on the Bootstrap Variance Estimate

c Adjusted mean utility score for respondents who use insulin minus adjusted mean utility score for respondents who do not. A negative score indicates lower utility scores for the group who uses insulin (i.e. a HRQL deficit).

* $p<0.05$ for between groups difference after adjusting for covariates

Table 4-3: Adjusted[a] Mean (95% CI) Difference in Overall and Single Attribute Utility Scores According to Comorbidities

	Cataracts		Heart Disease		Stroke		Depression	
	Respondents without Cataracts	Impact of Cataracts on HRQL: Mean (95% CI)[b] Difference[c]	Respondents without Heart Disease	Impact of Heart Disease on HQL: Mean (95% CI)[b] Difference[c]	Respondents without Stroke	Impact of Stroke on HRQL: Mean (95% CI)[b] Difference[c]	Respondents without Depression	Impact of Depression on HRQL: Mean (95% CI)[b] Difference[c]
Overall	0.61 (0.58, 0.64)	-0.03 (-0.06, 0.01)	0.63 (0.60, 0.67)	**-0.08*** **(-0.11, -0.05)**	0.67 (0.64, 0.70)	**-0.15*** **(-0.21, -0.10)**	0.68 (0.65, 0.71)	**-0.17*** **(-0.22, -0.12)**
Vision	0.93 (0.91,0.94)	**-0.02*** **(-0.04, -0.003)**	0.92 (0.90, 0.93)	0.00 (-0.01, 0.01)	0.93 (0.91, 0.94)	-0.02 (-0.04, 0.01)	0.93 (0.91, 0.94)	**-0.02*** **(-0.04, -0.003)**
Hearing	0.96 (0.94, 0.97)	0.00 (-0.01, 0.02)	0.96 (0.95, 0.98)	0.00 (-0.02, 0.01)	0.97 (0.96, 0.98)	-0.02 (-0.04, 0.01)	0.97 (0.95, 0.98)	-0.01 (-0.03, 0.01)
Speech	1.00 (0.99, 1.00)	-0.01 (-0.01, 0.00)	1.00 (0.99, 1.00)	0.00 (-0.01, 0.00)	1.00 (0.99, 1.00)	-0.01 (-0.01, 0.00)	0.99 (0.99, 1.00)	0.00 (0.00, 0.01)
Ambulation	0.88 (0.86, 0.91)	-0.02 (-0.05, 0.02)	0.89 (0.85, 0.89)	-0.02 (-0.04, 0.00)	0.94 (0.90, 0.95)	**-0.12*** **(-0.17, - 0.07)**	0.89 (0.85, 0.90)	-0.02 (-0.05, 0.01)
Dexterity	0.98 (0.97, 0.99)	-0.01 (-0.02, 0.01)	0.98 (0.97, 0.99)	**-0.01*** **(-0.02, -0.001)**	1.00 (0.99, 1.00)	-0.04 (-0.08, 0.01)	0.98 (0.97, 0.99)	0.00 (-0.01, 0.01)
Emotion	0.88 (0.87, 0.90)	0.00 (-0.01, 0.02)	0.90 (0.88, 0.91)	**-0.01*** **(-0.02, -0.002)**	0.91 (0.89, 0.92)	**-0.03*** **(-0.06, -0.01)**	0.96 (0.94, 0.97)	**-0.14*** **(-0.17, -0.10)**
Cognition	0.87 (0.85, 0.89)	0.01 (-0.01, 0.02)	0.89 (0.87, 0.91)	**-0.03*** **(-0.05, -0.01)**	0.91 (0.89, 0.92)	**-0.07*** **(-0.11, -0.03)**	0.91 (0.89, 0.92)	**-0.07*** **(-0.09, -0.04)**
Pain	0.74 (0.70, 0.77)	-0.02 (-0.05, 0.01)	0.77 (0.73, 0.81)	**-0.09*** **(-0.12, -0.05)**	0.75 (0.72, 0.79)	-0.06 (-0.12, 0.00)	0.78 (0.74, 0.81)	**-0.10*** **(-0.15, -0.05)**

a Adjusted for Age, Sex, Education, Marital Status, Race, other Sentinel Comorbidities (e.g. Depression, Stroke, Heart Disease, Cataracts), Number of Other Medical Conditions and Duration of Diabetes

b 95% Confidence Interval based on the Bootstrap Variance Estimate

c Adjusted mean utility score for respondents with the comorbidity minus adjusted mean utility score for respondents without the comorbidity. A negative score indicates lower utility scores for the group with the comorbidity (i.e. a HRQL deficit).

* $p<0.05$ for between groups difference after adjusting for covariates.

Table 4-4: Association between physician visits, hospitalizations, emergency room visits, severity of impairment on overall HUI3, demographic and clinical characteristics

Variable	**Physician Visits OR (95% CI)**	**Hospitalizations OR (95% CI)**	**ER Visits OR (95% CI)**
Overall HUI3			
No/Mild Impairment	**0.59 (0.48, 0.74)****	**0.67 (0.51, 0.89)***	**0.46 (0.24, 0.86)***
Moderate	**0.66 (0.51, 0.86)****	0.77 (0.55, 1.06)	0.59 (0.32, 1.10)
Severe Impairment[a]	-	-	-
Age Category			
18 to 44 years	0.95 (0.68, 1.32)	1.12 (0.70, 1.82)	2.06 (0.85, 4.96)
45 to 54 years	0.89 (0.65, 0.22)	1.03 (0.68, 1.58)	1.27 (0.51, 3.15)
55 to 64 years	0.97 (0.73, 1.27)	0.94 (0.66, 1.33)	1.38 (0.67, 2.86)
65 to 74 years	0.88 (0.69, 1.12)	0.98 (0.74, 1.31)	1.29 (0.64, 2.63)
75 years or older[a]	-	-	-
Sex			
Female	0.98 (0.81, 1.17)	0.98 (0.76, 1.27)	0.85 (0.53, 1.37)
Male[a]	-	-	-
Education			
Less Than High School	1.07 (0.77, 1.48)	**1.76 (1.11, 2.77)***	0.68 (0.30, 1.56)
High School	0.96 (0.68, 1.36)	1.40 (0.82, 2.35)	0.17 (0.05, 0.59)
Post-Secondary/ Trade	1.00 (0.72, 1.40)	1.29 (0.81, 2.03)	0.63 (0.28, 1.40)
School/College			
University[a]	-	-	-
Marital Status			
Married	1.02 (0.84, 1.24)	0.99 (0.77, 1.26)	0.83 (0.52, 1.35)
Not Married[a]	-	-	-
Aboriginal			
Aboriginal	1.44 (0.89, 2.32)	1.35 (0.77, 2.35)	0.69 (0.15, 3.28)
Not Aboriginal[a]	-	-	-
Duration of Diabetes			
≤ 2 years	1.01 (0.77, 1.31)	0.90 (0.72, 1.38)	1.19 (0.62, 2.28)
> 2 years, ≤ 6 years	**0.73 (0.56, 0.95)***	1.20 (0.67, 1.21)	0.82 (0.43, 1.52)
> 6 years, ≤ 13 years	0.99 (0.78, 1.28)	1.00 (0.88, 1.56)	1.20 (0.64, 2.21)
> 13 years[a]	-	-	-
Insulin Use	1.25 (0.95, 1.64)	**1.45 (1.07, 1.96)***	**2.04 (1.21, 3.44)***
Heart Disease	**2.02 (1.63, 2.50)***	**2.70 (2.13, 3.41)***	**1.72 (1.04, 2.84)***
Stroke	1.51 (0.99, 2.32)	**1.83 (1.19, 2.79)***	1.66 (0.62, 4.40)
Cataracts	1.26 (0.94, 1.69)	0.80 (0.59, 1.07)	0.62 (0.30, 1.27)
Depression	**2.20 (1.59, 3.07)***	**1.58 (1.07, 2.31)***	1.17 (0.55, 2.49)
Number of Medical Conditions	**1.27 (1.20, 1.35)***	**1.13 (1.04, 1.21)***	1.12(0.97, 1.30)

** $p<0.01$

* $p<0.05$

a – reference category

Figure 4-1: Algorithm for Differentiating between Individuals with Type 1 and Type 2 Diabetes

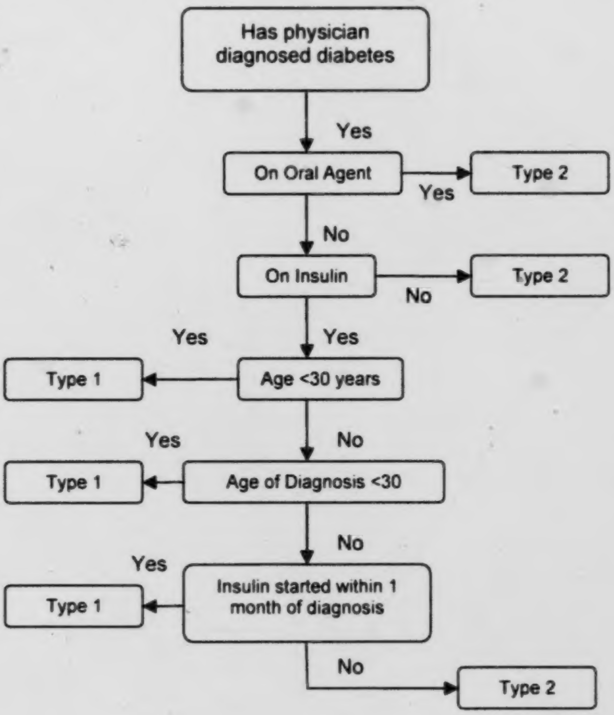
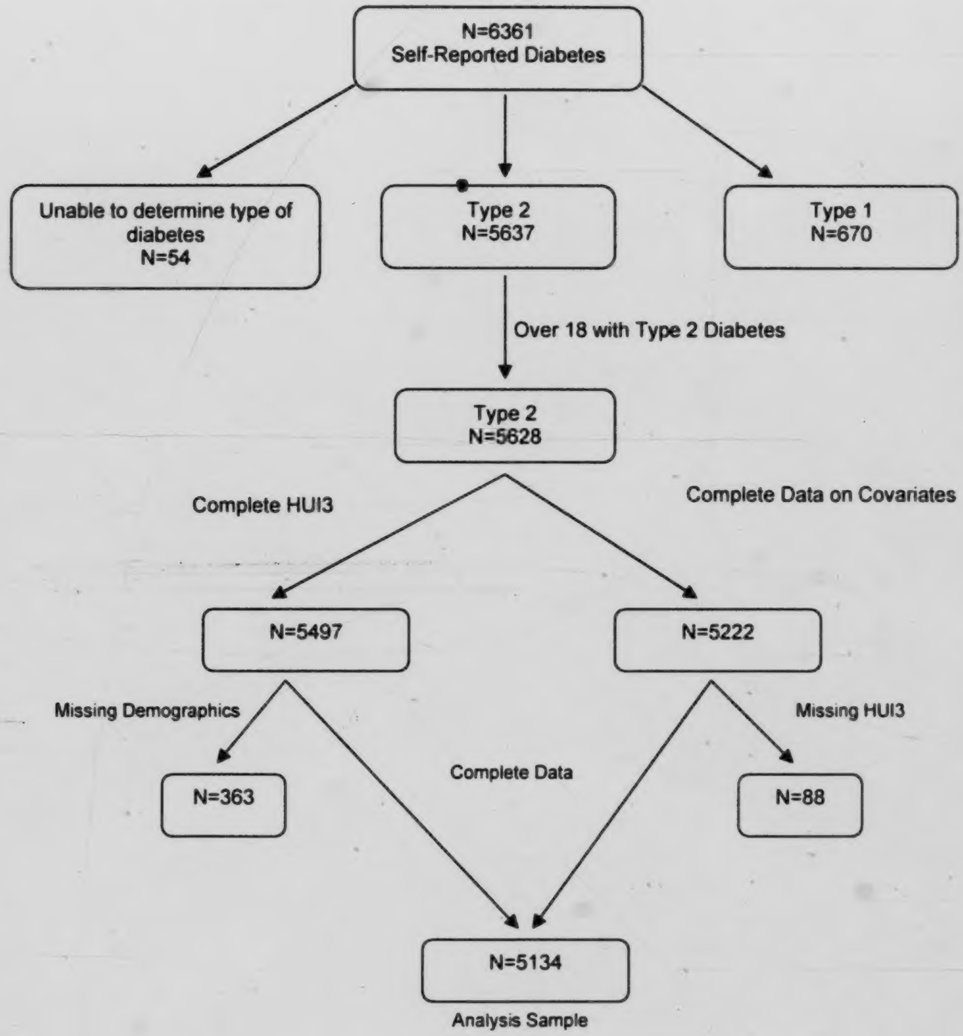


Figure 4-2: Survey Sample, Analysis Sample and Missing Data



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Chapter 5 – Determinants of Health of Canadians with Type 2 Diabetes[4]

5.1.0 Introduction

Diabetes affects approximately 5% of all Canadians aged 20 years or older, with the prevalence rising with age.(1) Type 2 diabetes accounts for 90% of the diagnosed cases of diabetes in Canada and can be associated with a substantial burden for individuals with the disease and their families. The health-related quality of life (HRQL) deficits reported by people with diabetes are generally attributed to the disease itself, its restrictive treatment regimens and its associated comorbidities. The observed heterogeneities in HRQL associated with diabetes, however, may be better explained in the context of a more holistic "determinants of health" framework since population health is not solely related to disease and treatment.(2;3)

5.1.1 Conceptual Scheme

The Population Health Framework developed by the Canadian Institute for Advanced Research (CIAR) was designed as a means of conceptualizing the determinants of health and their causal linkages (Appendix D).(4) It is intended to be a guideline for shaping policy and research(5), but due to the complexity of the specified relationships, it is difficult to operationalize from an analytical perspective. Thus, based upon CIAR's Population Health Framework, Hertzman, Frank, and Evans (in Evans et. al.'s "Why are some people healthy and others not?") proposed a conceptual scheme for organizing and analyzing the relative importance of individual level determinants of health specified in the Population Health Framework.(6) Using this conceptual scheme, the determinants of health are grouped into three major dimensions or domains: Stage of the Life Cycle, Subpopulation Partitions, and Sources of Heterogeneity (Table 5-1).(6) The dimensions relate to each other along three axes (Figure 5-1).

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[4] The research and analysis are based on data from Statistics Canada. The opinions expressed do not represent the views of Statistics Canada.

The Stage of the Life Cycle domain reflects the fact that age, in part, determines an individual's vulnerabilities or susceptibility to disease. In the conceptual scheme, the Stage of the Life Cycle is divided into four age categories that generally reflect the underlying vulnerabilities (Table 5-1).(6) In type 2 diabetes, the lower age boundary for the Chronic Disease Stage becomes less relevant as all individuals with type 2 diabetes have already developed a chronic disease. Further, comorbidities and complications occur frequently in people with type 2 diabetes, often even before diabetes is diagnosed, and negatively impact HRQL.(7;8) Approximately 60% of individuals have one or more complication, while almost one-quarter have two or more complications.(9)

The second domain of determinants of health are termed "Subpopulation Partitions"(Table 5-1), which are segments of the population across which heterogeneities in health status are observed.(6) Sex and socioeconomic status are examples of Subpopulation Partitions. Unique to type 2 diabetes, individuals who use insulin could be considered a Subpopulation Partition (specifically a special population) as they generally have HRQL deficits compared to those who do not use insulin.(10-12) The HRQL deficits associated with insulin use may simply relate to the observation that insulin users often have disease which has progressed further(10-12) or may relate to the increased treatment burden associated with insulin use.(13)

Sources of Heterogeneity are considered mechanisms which operate across Subpopulation Partitions and Stages of the Lifecycle and are an attempt to understand why we observe differences in HRQL between Subpopulation Partitions. In the conceptual scheme, the Sources of Heterogeneity are quite diverse and include behavioral and social determinants of health, as well as aspects of the environment, genetic endowment and differential access to health care (Table 5-1).

The general approach to studying factors associated with HRQL in diabetes has tended to focus on demographic and clinical factors (7;11-23), with less emphasis on individual life-style factors (such as stress), the social environment (such as social integration) and realized access to health care. Previous research has shown that demographic characteristics (i.e. age, sex, race, income and education) and clinical factors (i.e. complications and comorbidities, duration of diabetes, insulin) impact HRQL in diabetes and that some heterogeneities in HRQL in diabetes can be explained by these factors.(14) This is not surprising as a number of these variables are determinants of population health(4), but perhaps heterogeneities in HRQL in type 2 diabetes could be better explained using the more comprehensive Population Health Framework (Appendix D), operationalized as Hertzman et al.'s conceptual scheme. With the Stage of Life Cycle, Subpopulation Partitions, and Sources of Heterogeneity taken together, perhaps a better understanding of the factors driving HRQL deficits in type 2 diabetes could be gained. Alternatively, it is possible that the inclusion of more broad determinants of health does not enhance our understanding and that focusing on demographic and clinical factors may be sufficient.

5.1.2 Objectives

The purpose of this analysis was to assess (1) the magnitude of HRQL deficits associated with determinants of health in type 2 diabetes and (2) the contribution of Hertzman et al.'s Stage of Life Cycle, Subpopulation Partitions and Sources of Heterogeneities to the explained variance in HRQL in type 2 diabetes.

5.2.0 Research Design and Methods

5.2.1 Survey Design

Data from the Canadian Community Health Survey (CCHS) Cycle 1.1 were used in this analysis. The CCHS is a cross-sectional survey carried out across the 10 provinces and three territories of Canada in the population over age 12.(24) Data are collected on utilization of health services, determinants of health and health status on a two year cycle.(24) Cycle 1.1 had a large sample (N=131, 535), sufficient in size to give reliable estimates at the level of the health region.(24) The survey excludes individuals living on crown or reserve land, in institutions, members of the Canadian Armed Forces and some remote areas of the country. Approximately 98% of the Canadian population over 12 years of age is represented in the CCHS even with these exclusions.(24)

The CCHS has two different sampling frames, termed the *area frame* and *telephone frame*. For the area frame, the sample was drawn using a multistage stratified cluster design, based on the sampling frame designed for the Canadian Labour Force Survey.(25) Approximately 83% of the sample was taken from the area frame; however, in some health regions, the telephone frame was also used, comprising the remaining 17% of the sample.(26) Within the area frame, in approximately 82% of households, one respondent was selected at random to be surveyed with an in person interview, but in the remaining 18% of households, two respondents were randomly selected to be surveyed. Two respondents were chosen in order to over-represent individuals in the age group 12 to 19 years.(24) From the telephone frame, random digit dialing was used to select the sample and only one respondent was surveyed per household.

Data for Cycle 1.1 were collected between September 2000 and November 2001, using computer assisted interviewing. In total, the interview took approximately 45 minutes to complete. Overall, including both sampling frames, 41.4% of respondents used in these analyses had telephone interviews, 56.7% had in person interviews and 1.9% had a combination of techniques.

Proxy reporting was permitted for certain components of the interview, but many components were deemed only appropriate for self-response. Proxy reporting was permitted only if the respondent selected for the survey would not be available for the entire period of data collection, was unable to respond due to physical or mental illness preventing the interview or had a language barrier.(26) At the end of Cycle 1.1, the overall response rate was 84.7%.(26)

5.2.2 Sample

Approximately 6361 respondents self-reported having a diagnosis of diabetes, representing a weighted percentage of 4.1%. An algorithm based upon age, treatment regimen, duration of time from initial diagnosis to initiation of insulin therapy, and age at diagnosis was used to categorize individuals as having type 1 or type 2 diabetes (Figure 5-2). The criteria of less than 30 years old and being placed on insulin immediately has been used previously to classify individuals as having type 1 diabetes.(27) As well, being on an oral agent to manage diabetes has previously been used to categorize respondents as having type 2 diabetes.(28;29) Of the respondents who were categorized as having type 2 diabetes, 4678 (83.1%) had complete data and were included in this analysis (Figure 5-3).

5.2.3 Health Utilities Index Mark 3 (HUI3)

HUI3 is a preference-based measure of HRQL that uses a multiplicative utility function to assign valuations to different health states.(30;31) Using the multi-attribute approach, health states are defined by a classification system that includes a set of dimensions or attributes of HRQL, with a number of different levels of functioning for each attribute. In the HUI3 system, eight attributes, including vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain, define health status. Each attribute has five or six levels, creating 972,000 unique HUI3 health states (Appendix C).(30) The overall utility function for the HUI3 was derived from visual analogue scale and standard gamble techniques and responses from random samples from the general population in Hamilton, Ontario, Canada.(30) Overall scores on the HUI3 range from -0.36 to 1.0, with -0.36

representing the utility of the worst possible HUI3 health state, 0.0 representing dead and 1.0 representing perfect health.(30) Differences of greater than 0.03 for HUI3 overall scores are considered to be clinically important.(32) Assessment of health status using the HUI3 can be based upon current or usual health. In the versions of the questionnaire used to assess current health status, a specific duration of recall is given: one, two or four weeks. Population survey applications of the HUI3 typically assess usual health status, and no duration of recall is given.(32) In the CCHS, the HUI3 was administered as a 31-item, questionnaire with no specific recall period (i.e., "Are you usually able to…").

5.2.4 Determinants of Health

Table 5-2 summarizes the independent variables used in the analysis, the manner in which they were operationalized and their categorization into the three domains in Hertzman's et al conceptual scheme.

5.2.4.1 Stage of Life Cycle

5.2.4.1.1 Age

Consistent with the exponential increase in comorbid conditions over the age of 70(33), previous research using the HUI3 has detected a nonlinear relationship between age and HRQL.(34;35) Thus, age was operationalized in the quadratic form (i.e. $b_1$age + $b_2$age^2). Due to collinearity between age and its square, age was analyzed as a deviation from its mean (i.e. mean centered: age – 61.55) and the square of this variable [(age - 61.55)^2].(36) This procedure has no effect on estimates of other variables in the analyses. It simply reduces the correlation between a variable and its square from approximately one to approximately zero(36), which can correct issues related to the high correlation, or collinearity, such as inflation of standard errors of a variable or its square and difficulties estimating the beta coefficient of either variable.

5.2.4.1.2 Sentinel Comorbid Medical Conditions

During the chronic disease Stage of Life Cycle, degenerative diseases such as heart disease, stroke, and arthritis are considered the primary threats to health in Hertzman et al.'s conceptual scheme and, as such, are of particular significance.(6) Moreover, heart disease and stroke are two common macrovascular comorbidities in diabetes (7;8;37;38) that are associated with large HRQL deficits(7;8;39-41). Further, it is relatively common for individuals with type 2 diabetes to have osteoarthritis since both conditions are more common in older adults and those who are obese.(42) Past research has demonstrated that comorbid arthritis or osteoarthritis is associated with significant HRQL deficits in diabetes.(34;43) In addition to degenerative diseases, depression is a relevant comorbidity to consider since diabetes is associated with an approximately two-fold increased risk of depression(44) and depression has been associated with a significant additional HRQL deficits in diabetes.(43;45) Thus, of the 25 chronic conditions included in the CCHS, stroke, heart disease, osteoarthritis and depression were of particular interest.

The presence of heart disease, stroke and arthritis was based upon self-report from a direct question in the CCHS which asks: "We are interested in long term conditions that have lasted or are expected to last six months or more and that have been diagnosed by a health professional. Do you have…," followed by a list of common chronic conditions.

Respondents who reported a diagnosis of arthritis were further asked the specific type of arthritis they had. For depression, the CCHS used the Composite International Diagnostic Interview Short Form for Major Depression (CIDI-SFMD) to assess the probability of a major depressive disorder. A probability of 0.90 is considered consistent with a diagnosis of a depression and is accordance with the DSM-IV diagnostic criteria for Major Depressive Disorder.(46)

5.2.4.1.3 Number of Medical Conditions

To assess the HRQL deficits associated with other medical conditions, we included the total number of self-reported medical conditions other than heart disease, stroke, depression and osteoarthritis.

5.2.4.1.4 Duration of Diabetes

Duration of diabetes was determined from the respondents' age and self-reported age of diagnosis of diabetes. Respondents were then grouped into quartiles of duration of diabetes: less than 2 years, 2.0 to 6.0 years, 6.0 to 13.0 years and 13.0 years or greater.

5.2.4.2 Subpopulation Partitions

5.2.4.2.1 Socioeconomic Status

As a significant proportion of respondents (approximately 11%) were missing data on income, other markers were used to operationalize socioeconomic status in the conceptual scheme including education, household social assistance, and household food security. Highest level of education of each respondent was assessed in four categories:

less than secondary graduation, secondary graduation, other post-secondary education (e.g. diploma/certificate from a trade school, some community college), and college or university degree. Receipt of social assistance was determined by self-reported social assistance as a source of total household income in the past 12 months. Three questions determined whether respondents had food insecurity in the past twelve months. Food insecurity was defined as (1) not having enough food to eat or (2) not eating the quality or variety of foods that the respondent wanted due to lack of money.

5.2.4.2.2 Insulin Use

Questions regarding insulin use were included in the core survey content and in the optional survey content, making it possible to categorize almost all respondents as insulin users or nonusers.

5.2.4.2.3 Geographic Location – Rural vs Urban

According to Statistics Canada, an urban area was defined as a continuously built-up area with a population concentration of 1,000 or more, with a population density of 400 or more per square kilometre based on the previous census. To be considered continuous, the built-up area could not have a discontinuity exceeding two kilometres.(26)

5.2.4.2.4 Sex

Sex was included as a determinant of health in the model. Respondents were categorized as male or female.

5.2.4.2.5 Ethnicity or Race

Respondents were categorized as Aboriginal or Non-aboriginal, according to a question that asked respondents their cultural or racial background.

5.2.4.3 Sources of Heterogeneities

5.2.4.3.1 Individual Lifestyle Factors

Body mass index was calculated from self-reported height in meters (m) and weight in kilograms (kg); specifically, BMI = kg/m^2. Respondents were categorized as obese (BMI ≥ 30.0) or not obese (BMI < 30.0).(47) Smoking status was derived from responses to four questions pertaining to current and past smoking habits. Respondents were categorized as current smokers or nonsmokers. Respondents who consumed five drinks or more on one occasion more than once a month were considered heavy drinkers.(48) For physical activity, the CCHS categorizes respondents as inactive, moderately active, or active based on energy expenditure level. Energy expenditure level was derived from 47 questions regarding participation in specific activities and individual report on participation in other activities.

Self-perceived life stress was used as a measure of ability to cope. Respondents were asked to rate the amount of daily stress in their lives with response options ranging from "not at all stressful" to "extremely stressful" on a 5-point likert scale. Response options were collapsed to create three categories: not at all stressful, not very stressful/a bit stressful and quite a bit stressful or extremely stressful.

5.2.4.3.2 Physical Environment

The presence or absence of a family member who smoked inside the home was used as a measure of exposure to second hand smoke.

5.2.4.3.3 Social Environment

Sense of belonging to the community and marital status were used to assess the social environment. Sense of belonging to the local community was assessed on a 4-point likert scale with response options of "very strong", "somewhat strong", "somewhat weak" and "very weak". This variable was operationalized in four categories. For marital status, respondents were categorized as "married/partnership" or "not married". The married category included respondents who reported being married, common-law or living with a partner, while not married included respondents who were single, widowed, separated or divorced.

5.2.4.3.4 Differential Access to Health Care

Access to medical care was assessed using two variables: whether respondents had a regular medical doctor and self-perceived unmet healthcare needs. For self-perceived unmet self-care needs, respondents were asked, "During the past 12 months, was there ever a time when you felt the you needed health care but did not receive it?' with yes or no response options.

5.2.5 Analysis

5.2.5.1 Analysis of Cases with Missing Data

Analyses were performed on cases with complete data; however, some of this data had been imputed by Statistics Canada during data processing. For interviews that were completed by proxy (6.3%), imputation using the "nearest neighbour" imputation method (i.e. hot-decking) was used to handle missing data for a pre-defined set of variables.(24) Certain modules or items were not considered appropriate for imputation and, thus, those items were left as missing in the survey (e.g. distress, work stress). As well, when imputation could not improve data quality (i.e. produced poor estimates for those variables), responses were coded as missing.(26) Imputation was not used for non-proxy respondents who declined to answer particular questions. Thus, not all missing values were imputed by Statistics Canada. We did not employ additional imputation methods for variables where Statistics Canada had opted not to impute data.

T- and Chi-Square tests were used, where appropriate, to compare the demographic characteristics of respondents who were excluded from the analysis because they were missing only HUI3 scores (n=76). These respondents had complete data on all other variables of interest (Figure 5-3). The overall HUI3 scores of the analysis sample (n=4678) were compared to those of respondents who were excluded from the analysis due to missing data on either the Stage of Life Cycle variables, Subpopulation Partitions or Sources of Heterogeneity (n=819).

5.2.5.2 Objective One – Determinants of Health

The clinical importance (i.e., magnitude of the unstandardized regression coefficients) and statistical significance of the HRQL deficits associated with each determinant of health were first assessed with bivariate regression analyses. The correlation between each determinant of health and overall HUI3 score was determined from these bivariate analyses. A multiple regression model that included all determinants of health was then used to operationalize the entire conceptual scheme and control for the relationships among determinants of health. The clinical importance and statistical significance of each determinant of health in the overall model was then assessed. A regression coefficient with a bootstrap confidence interval that excluded zero was considered statistically significant (i.e. $p<0.05$). To assess the degree of collinearity in the overall model, the tolerance of each independent variable was evaluated (i.e. the proportion of variance in the independent variables unexplained by the other independent variables). As a general guideline, when the tolerance of a variable is less than 0.20, collinearity may be a problem.(49) As each determinant of health had a tolerance that exceeded 0.20, collinearity in the overall model was not thought to be problematic.

5.2.5.3 Objective Two – Contribution of Each Domain

The proportion of explained variance (i.e., R^2) in HRQL explained by each domain was determined from three regression models that each contained the determinants of health for their respective domains (Stage of Life Cycle, Subpopulation Partitions, and Sources of Heterogeneities). To determine the unique contribution to the explained variance of a particular domain, the R^2 change was calculated between a model containing the other two domains and a model with all three domains. For example, to determine the unique contribution of the Stage of Life Cycle Variables, the Stage of Life Cycle variables were added to a model containing Subpopulation Partitions and Sources of Heterogeneity and the R^2 change between the two models was calculated. The same process was used to determine the unique contributions of the Sources of Heterogeneity and Subpopulation Partitions. An R^2 change with an F-Statistic whose p-value was less than 0.05 was considered statistically significant. Collinearity within each block was assessed in the same manner employed in the overall model and determined not to be problematic.

5.2.5.4 Weighting and Variance Estimates

The multistage stratified cluster design of the CCHS created an unequal probability of being selected for inclusion into the survey, which, unaccounted for, can bias point estimates (e.g. of regression coefficients, means, etc.) and underestimate the variance. Thus, normalized sampling weights were applied to the analysis in order to produce unbiased point estimates.(26) Normalized sampling weights do not adjust for clustering or stratification(26); thus, bootstrap variance estimates were used to estimate 95% confidence intervals for the regression coefficients.(50) Consistent with Statistics Canada's policies for disclosure, data pertaining to any cell with a weighted or unweighted frequency of less than five were suppressed.

5.3.0 Results

5.3.1 Sample Characteristics

The average (SD) age of respondents included in the analysis was 61.6 (13.3), with an average duration of diabetes of 9.3 (9.8) years (Table 5-3). Heart disease and osteoarthritis were the two most common comorbidities of interest, affecting 20.6% and 19.4% of respondents, respectively. Failure to complete high school was relatively common (42.4%). Only a small proportion of respondents were Aboriginals (1.8%). While approximately 7.5% of respondents reported receiving social assistance, 15.5% reported some food insecurity in the previous 12 months. Physical inactivity (64.6%) and obesity (36.4%) were prevalent in this sample. The vast majority of respondents had a regular medical doctor (96.0%), but 12.7% of the sample felt that they had unmet healthcare needs. The overall HUI3 scores was 0.78 (0.26).

5.3.2 Missing Data

The HUI3 scores for respondents who were excluded from the analyses due to missing data on the determinants of health (n=819) (Figure 5-3) were significantly lower than the overall HUI3 scores of respondents with complete data (difference between groups = -0.14; 95% CI: -0.17, -0.10, p<0.05). The majority of differences for comparisons between respondents who had complete data on the determinants of health, but were missing data on the HUI3 (n=76) (Figure 5-3) and respondents included in the analysis (n=4678) were not statistically significant. Those who were missing HUI3 were, however, more likely to report a weak sense of belonging to the community (p=0.01), food insecurity in the past

12 months (p=0.001), heart disease (p=0.04), stroke (p=0.04) and osteoarthritis (p=0.02) and less likely to report being married (p=0.03).

5.3.3 Mean Centered Age

As previously explained, age was operationalized as a mean centered variable in order to reduce problems with collinearity between itself and its square as a quadratic function in the regression models. Figures 5-4a and 5-4b demonstrate that mean centering had little effect on the overall nature of the nonlinear relationship between age and HRQL, i.e. the shape of the curves were basically the same, although not identical. The two quadratic equations result in predicted overall HUI3 scores that differ, on average, by approximately 0.024 units, with larger predicted differences observed for older ages. Collinearity was particularly problematic in the multiple regression analysis, where the tolerance of age and its square was 0.02 for each variable (a tolerance of less than 0.20 is a concern). In this analysis, collinearity also created problems estimating the standard error of the age variable as evidenced by the fact that its standard error was five times higher prior to mean centering than after. Thus, it was apparent from both the bivariate and multiple regression analyses that mean centering was necessary.

5.3.4 Objective One – Determinants of Health

5.3.4.1 Bivariate Associations

5.3.4.1.1 Stage of Life Cycle

All Stage of Life Cycle variables had statistically significant and clinically important bivariate associations with HRQL (Table 5-4). With the exception of number of medical conditions, the correlations between the Stage of Life Cycle variables and HRQL were weak. Of the Stage of Life Cycle variables, number of medical conditions was the variable that individually accounted for the most variance in HRQL. The comorbidities of interest were associated with clinically important deficits in HRQL, the largest of which were related to depression and stroke. Respondents who had the longest duration of diabetes had significantly worse HRQL than any other quartile (Table 5-4). The hypothesized nonlinear association between age and HRQL was supported (Figure 5-4c). For interpretation purposes, in Figure 5-4c, the age variable was converted back to natural units and plotted against the predicted overall HUI3 obtained from the mean centered quadratic. The nature of the nonlinear relationship between age and HRQL was interesting in that compared to respondents aged 18, HRQL was greater between the ages of 19 to 45 after which HRQL declined (Figure 5-4c).

5.3.4.1.2 Subpopulation Partitions

Weak correlations were observed between the Subpopulation Partitions and HRQL (Table 5-4). Food insecurity and social assistance were the Subpopulation Partitions that explained the largest proportion of variance in HRQL (6.0% and 4.0%, respectively). The largest HRQL deficits across Subpopulation Partitions were reported for respondents who reported food insecurity and receiving social assistance. A gradient was observed across level of education; respondents with less than secondary education had the largest HRQL deficits relative to respondents with university degrees (-0.11, 95% CI: -0.14, -0.07). Males reported better HRQL than females (0.06, 95% CI: 0.03, 0.08) and insulin use was associated with a clinically important deficit (-0.10, 95% CI:-0.13, -0.06).

5.3.4.1.3 Sources of Heterogeneity

Again, only weak correlations were observed among the determinants of health and HRQL, with relatively small proportions of variance explained by any single determinant of health. Many individual lifestyle factors had clinically important bivariate associations with HRQL. The largest deficits among the Sources of Heterogeneity were associated with high levels of stress, self-perceived unmet healthcare needs and weak sense of belonging.

5.3.4.2 Overall Determinants of Health Framework

When the conceptual scheme was operationalized in its entirety (Stage of Life Cycle, Subpopulation Partitions and Sources of Heterogeneity in a single model), the magnitude of a number of the coefficients decreased significantly, but the basic patterns within each domain persisted (Table 5-5). Across all of the determinants of health included in the model, stroke and depression were associated with the largest deficits and were nearly four times the clinically important difference of 0.03. Clinically important deficits were also associated with socioeconomic status (food insecurity, social assistance and failure to complete a secondary education). Within the Sources of Heterogeneity, the largest differences between respondents were observed according to sense of belonging to the community, life stress, and self-perceived unmet healthcare needs. The variables in the conceptual scheme, as a whole, explained 36% of the variance in HRQL and had a strong association with HRQL (multiple correlation = 0.60).

5.3.5 Objective Two – Contribution of Each Domain

Taken together, the Stage of Life Cycle variables explained the most variance (27.0%) of the three domains and had a moderate multiple correlation with HRQL (Models 1 through 3, Table 5-5). The Sources of Heterogeneity explained 16% of the variance in HRQL and also had a moderate multiple correlation with HRQL (Model 3, Table 5-5). The largest unique contribution to the explained variance in HRQL was that of the Stage of Life Cycle variables (15.0%), followed by Sources of Heterogeneity (6.0%) and Subpopulation Partitions (2.0%) (Table 5-5).

5.4.0 Discussion

Type 2 diabetes is a chronic medical condition in which many factors potentially influence HRQL or health status, some of which are disease related, but many of which relate to demographic, social characteristics and health behaviors. Using population based data from the Canadian Community Health Survey, we constructed a model of the multiple determinants of health in type 2 diabetes.

In the bivariate analysis, we explored heterogeneities in HRQL related to each variable that was used to operationalize the Population Health Framework. While the inter-relationships among determinants of health were not considered in the bivariate analysis, these analyses did confirm the hypothesized role of a number of determinants of health in type 2 diabetes. Subsequently operationalizing the conceptual scheme as a whole allowed us to control potential confounding among determinants, enabling us to better assess the magnitude of the deficits associated with particular determinants, which is the intent of Hertzman et al.'s conceptual scheme.

It was evident from the overall model that several of the comorbidities of interest (i.e. stroke and depression) were associated with the largest HRQL deficits (-0.11 for each), even after considering the impact of socioeconomic and behavioral determinants of health. The clinically important deficits associated with comorbidities demonstrate that prevention (where possible) and management of comorbidities could be vital to preserving or improving HRQL for people with type 2 diabetes. From a clinical perspective and broader health policy perspective, efforts at primary and secondary prevention of heart disease and stroke could have a significant impact on HRQL. Better efforts may also be needed in screening and treatment of depression in diabetes, given the magnitude of the deficit associated with this comorbidity.

When looking at the Subpopulation Partitions, the clinically important deficits associated with the two markers of income (social assistance and food insecurity) were also of interest (-0.07 and -0.08, respectively). Income and social status have been recognized as two of the most important determinants of health in the Canadian population.(2;3) Specifically in diabetes, income is an important predictor of social functioning and mental health; thus, this observation is consistent with previous research.(10) It was interesting to note, however, that the two markers appeared to capture somewhat different phenomena as they were both independently associated with clinically important deficits that reached statistical significance. While social assistance may have captured respondents with low income as intended, it is possible that food insecurity reflected the impact of poor nutrition in diabetes on overall health, in addition to low socioeconomic status.

Education was also a clinically important variable in the multiple regression analysis, confirming that it is, indeed, an important determinant, even independent of its association with income.(4) A relationship between education and physical health, physical and social functioning, and mental health in diabetes has been demonstrated previously.(10;14) It has been suggested that the relationship between education and HRQL is in part attributable to the association between higher levels of education and healthier lifestyles, including refraining from smoking, higher levels of physical activity and better access to healthy foods.(3) Despite controlling for a number of these factors, the relationship between education and HRQL persisted. In diabetes, it has been suggested that education may also influence diabetes-related knowledge, ability to communicate with healthcare providers, treatment choices and ability to adhere to complex self-care regimens, which in turn affect HRQL.(51) This could perhaps better explain why we found heterogeneities in HRQL according to education in type 2 diabetes.

The multiple regression analysis did reveal that a number of bivariate relationships between Subpopulation Partitions and HRQL were likely confounded. Heterogeneities in HRQL observed in the bivariate analysis according to Aboriginal Status, for example, did not persist in the overall model. This may seem counter-intuitive as Aboriginals are an ethnic group in Canada for whom disparities in health status are often observed.(52;53) In general, Aboriginals are more likely to rate their health as poor, and have shorter life expectancies, higher mortality rates, and higher rates of diabetes, hypertension, arthritis, and heart disease than the general Canadian population.(52;53) Aboriginal people with diabetes are more likely to develop macrovascular and microvascular complications and do so after shorter disease duration than the general population with diabetes.(54) However, controlling for comorbidities, socioeconomic status and other behavioral determinants of health may have reduced the differences in HRQL according to this particular Subpopulation Partition.

The Sources of Heterogeneity produced interesting results. Sense of belonging to the local community and marital status were used to assess the respondents' social environment. While marital status was not associated with HRQL in the overall model, one of the largest differences in HRQL was observed between respondents who reported a weak sense of belonging to the local community and respondents who reported a strong or somewhat strong sense of belonging. Sense of belonging has been previously found to relate to self-rated health in the Canadian population, (55) where Ross considered sense of belonging to be a measure of social capital, despite the fact that it was evaluated as an individual level variable, as it was in this study. This may not be consistent with the broader concept of social capital, though there is some debate over the level at which this variable should be analyzed.(56) Perhaps when analyzed at the individual level, sense of belonging may better reflect social integration (i.e. a measure of the degree to which individuals are socially isolated).(57) Marital status has also been considered a measure of social integration(57), which may explain, in part, why marital status was not associated with clinically important deficits in the overall model.

Life stress was another Source of Heterogeneity where clinically important differences were observed between respondents. Respondents who felt their lives were 'quite a bit stressful' or 'extremely stressful' experienced HRQL deficits nearly three times the clinically important difference relative to those who felt their lives were 'not at all stressful'. Stress is recognized as a determinant of health in the general population. High levels of stress may be particularly problematic, however, for individuals with diabetes as stress is associated with poor glycemic control.(58;59) This might explain the magnitude of the deficit associated with high stress levels observed in this sample of respondents with type 2 diabetes.

To measure access to healthcare services we used two markers: having a regular medical doctor and self-perceived unmet healthcare needs. The vast majority of the sample (96.0%) had regular medical doctor. The health status of the small number of respondents who did not have a regular medical doctor did not appear to suffer as a result. Having a regular medical doctor did not guarantee that healthcare needs would be met, however, as almost 13% of respondents reported unmet needs, while only 4.0% did not have a regular medical doctor. Unmet healthcare needs were associated with clinically important deficits in HRQL. This is finding is important for health policy makers to consider, given that often the reasons that patients cite for unmet healthcare need are beyond the control of the patient and clinician, such as excessive wait times and services not being available in an area.(60) Unmet health care needs increased in the Canadian population between the 1995 and 2001.(60) Increasingly, features of the healthcare system are cited as the reason for these unmet needs.(60)

Overall, the multiple regression results demonstrated that a broad range of determinants of health are important in type 2 diabetes, but were associated with deficits of various magnitudes. Knowing the determinants of health associated with clinically important HRQL deficits is relevant to researchers, health policy and clinicians. The strategies that are developed to deal with the 'diabetes epidemic' should consider the segments of the population with diabetes that experiences the greatest burden. Given that comorbidities and low socioeconomic status were particularly burdensome, these areas may warrant particular attention from a policy perspective.

The large number of determinants of health in the multiple regression analysis and the possibility of relationships between these determinants of health created the potential for collinearity in the overall model and within each block. The failure to confirm the bivariate associations between several of the determinants of health and HRQL in the overall multiple regression model suggested that there was, indeed, some degree of collinearity between determinants of health. We did not feel that collinearity was problematic to the extent of creating estimation problems, however, as the tolerance of all independent variables was well above the minimally acceptable threshold.

Of the three domains of determinants of health in the conceptual scheme, Stage of Life Cycle variables alone accounted for the largest proportion of variance in HRQL. Stage of Life Cycle was operationalized in a manner somewhat specific to diabetes as this domain included the comorbidities that occur more frequently in diabetes, as well as duration of diabetes. Thus, it is not clear if Stage of Life Cycle would be the dominant domain in the general population or in other chronic diseases. Further, using cross-sectional precludes us from definitively stating that the Stage of Life Cycle variables were the most important determinants of health in diabetes, as we were unable to assess causal relationships among variables. For example, cross-sectional data cannot capture the fact that Aboriginals, individuals who smoke or who are sedentary may be more likely to develop comorbidities such as heart disease.(54;61) Thus, the full explanatory power of the Subpopulation Partitions and Sources of Heterogeneity may not have been captured in this analysis.

Overall, Subpopulation Partitions accounted for the least variance in HRQL and explained little unique variance in HRQL despite the fact that clinically important differences in HRQL were noted according to insulin use and socioeconomic status (social assistance, food insecurity and education). Sources of Heterogeneity accounted for less variance than Stage of Life Cycle, but it should be pointed out that the ability to operationalize this domain was somewhat limited. While the CCHS included detailed information on individual life-style factors, it did not contain much information on the physical environment, social environment or differential access or response to health care services. Social support scales were included, but as optional content, limiting the usefulness of these data for our analyses. Perhaps if the Sources of Heterogeneity were more fully operationalized, the domain would have explained a larger proportion of the variance. As the conceptual scheme was currently operationalized, no treatment or clinical variables were included (other than insulin). Such variables (e.g. whether a patient was treated to a target for blood glucose or blood pressure or received appropriate drug therapy) would be considered differential access or response to therapy. These variables may have made a contribution to the Sources of Heterogeneity.

A number of study limitations should be noted in this analysis. The algorithm used to distinguish between respondents with type 1 and type 2 diabetes has not been previously validated. A number of the criteria in the algorithm have been used previously(27-29), but the algorithm as a whole has not. We were reasonably confident the algorithm accurately classified respondents, however, as categorization of type 1 and type 2 diabetes produced by the algorithm was 10% and 90%, which is generally recognized as the distribution of type 1 and type 2 diabetes in Canada.(62)

The cross-sectional nature of the data limited our ability to assess temporal relationships between HRQL and the determinants of health; thus, it is possible that a number of determinants of health were endogenous in the model. For example, in our analysis, social assistance (a marker of low socio-economic status) was modeled as a cause of poor HRQL. It is also possible that poor health and HRQL may cause low income, though past research has demonstrated that the effect of socioeconomic status on HRQL is the stronger relationship.(6;63;64)

Another potential limitation was related to the accuracy of self-reported data on a number of determinants of health including medical conditions, alcohol use, BMI, duration of diabetes, and level of physical activity. Although the questions regarding medical conditions specified that the condition have been diagnosed by a health professional, there remained potential for individuals to over- or under-report any medical condition. BMI may have been subject to bias in that it was determined from self-reported height and weight. The accuracy of this data could be questionable; thus, we chose to operationalize BMI as a dichotomous variable, either above or below 30.0. As with any health behavior, questions regarding alcohol consumption may have been answered in a socially desirable manner. The validity of self-reported level of physical activity may be questionable, but it should be emphasized that the physical activity index was based on detailed responses to 47 questions on participation in specific activities and participation in other activities. This reduced the need to recall the activities in which the respondents participated; however, duration of time spent in each activity may have been subject to inaccurate recall or social desirability.

Missing data were somewhat problematic. Approximately 17% of respondents were missing data, which lead to their exclusion from the analysis. Certain covariates (i.e. sense of belonging, physical activity and depression) had a relatively large number of respondents with missing data. Respondents who were missing data on covariates tended to have worse HRQL. Demographic differences also existed between respondents with complete and missing HUI3 scores. Regardless, we chose to include all of the variables we had originally proposed since the intent of this analysis was to operationalize Hertzman et al.'s conceptual scheme as fully as possible. Missing data could be missing for a number of reasons. If a non-proxy respondent refused to answer, the response was not imputed. Some questions were not considered appropriate for interviews completed by proxy (approximately one-third of the survey). For a number of those items, data were then imputed, but not in all instances (e.g. physical activity) as Statistics Canada did not consider some variables appropriate for imputation or had attempted to do so, but had obtained unsatisfactory results. It is not clear what impact missing data had on the analysis, but may limit the generalizability of the results.

In light of these limitations, the strengths of this analysis should also be noted. We modeled the determinants of health in type 2 diabetes using a large sample, representative of 98% of the Canadian population. Further, we used a broad framework, rather than limiting our analysis to medical and disease-related factors. Without using this framework, we may not have included a number of variables that were associated with clinically important HRQL deficits, sense of belonging and life stress, in particular. Further, by including multiple domains of determinants of health, we were able to confirm that previously detected relationships, such as those seen between HRQL and comorbidities or insulin use were not merely confounded by socioeconomic or behavioral factors. A final strength of this analysis was the use of the HUI3 as the measure of HRQL, a measure that we have previously shown to have construct validity in this population.(65;66)

5.5.0 Conclusions

Overall the analysis confirmed that many of the determinants of health specified in the Population Health Framework were, indeed, important in type 2 diabetes. Clinically important heterogeneities in HRQL were observed for people with diabetes and stroke or depression, emphasizing the importance preventing and managing comorbidities and complications in type 2 diabetes. Social and behavioral determinants of health (socioeconomic status, life stress and sense of belonging) were also important in type 2 diabetes, however, demonstrating that more than purely medical factors impact the health of individuals with type 2 diabetes. Thus, employing a Population Health Framework, operationalized with the broad determinants of health it encompasses, is an important and feasible approach to understanding HRQL in type 2 diabetes.

Table 5-1: Conceptual Scheme for Operationalizing the Population Health Framework

Stage of Life Cycle	**Subpopulation Partitions**	**Sources of Heterogeneities**
Perinatal : preterm to 1 year	Socioeconomic status	Individual life-style
Misadventure: 1 to 44 years	Ethnicity/migration	Physical environment
Chronic disease: 45 to 75 years	Geographic	Social environment
Senescence: 75 years or older	Male/Female	Differential access or response to health care services
	Special Populations[A]	Reverse Causality
		Differential susceptibility

[A] Special populations include groups not defined by one of the other subpopulation partitions (i.e. socioeconomic status, ethnicity migration, geographic location, and sex), but who share a particular characteristic that is related to patterns in health status.

Table 5-2: Independent Variables and Their Operationalization in the Conceptual Scheme

Variable	Operationalization in the Analysis	Reference category
Stage of Life Cycle		
Age	Continuous – Mean Centered Quadratic	Not applicable
Heart Disease	Categorical – Dichotomous dummy	No heart disease
Depression	Categorical –Dichotomous dummy	No depression
Osteoarthritis	Categorical – Dichotomous dummy	No Osteoarthritis
Stroke	Categorical – Dichotomous dummy	No History of Stroke
Number of Other Medical Conditions	Continuous – Linear	
Duration of Diabetes	Categorical – Three dummy variables	Longer than 13 years
Subpopulation Partitions		
Socioeconomic Status		
Education	Categorical – Three dummy variables	College or University Degree
Social Assistance	Categorical – Dichotomous dummy	Not receiving social assistance
Food Insecurity	Categorical – Dichotomous dummy	No food insecurity
Ethnicity		
Aboriginal Status	Categorical – Dichotomous dummy	Non-aboriginal
Male/Female	Categorical – Dichotomous dummy	Male
Geographic Location		
Rural versus Urban	Categorical – Dichotomous dummy	Urban
Special Populations		
Insulin User	Categorical – Dichotomous dummy	Not using insulin
Sources of Heterogeneities		
Individual Life-Style		
Body Mass Index (BMI)	Categorical – Dichotomous dummy	BMI less than 30.0
Smoking status	Categorical – Dichotomous dummy	Non-smoker
Alcohol Use	Categorical –Dichotomous dummy	Not a heavy drinker
Physical Activity	Categorical – Two dummy variables	Inactive
Stress	Continuous – Two dummy variables	Not at all stressful
Physical Environment		
Smoking in house	Categorical – Dichotomous dummy	Family member does not smoke in house
Social Environment		
Sense of belonging	Continuous – Three dummy variables	Weak
Marital Status	Categorical – Dichotomous dummy	Not Married
Differential Access or Response to Health Care Services		
Regular medical doctor	Categorical – Dichotomous dummy	No regular medical doctor
Unmet Medical Need	Categorical – Dichotomous dummy	No Unmet needs

Table 5-3: Demographic Characteristics of Analysis Sample

	N=4678
Stage of Life Cycle	
Age – Mean (SD)	61.6 (13.3)
Duration of Diabetes – Mean (SD)	9.3 (9.8)
Median (Interquartile Range)	6.0 (2.0-13.0)
Number of Medical Conditions[A] – Mean (SD)	2.7 (1.7)
Has Osteoarthritis (% Yes)	19.4
Suffers the Effects of Stroke (% Yes)	4.8
Has Heart Disease (% Yes)	20.6
Predicted Probability of Depression > 0.90 - %	7.2
Subpopulation Partitions	
Sex – (% Male)	51.7
Level of Education - %	
Less than secondary	42.4
Secondary graduation	16.3
Some post-secondary, college, trade school	29.3
University degree	12.0
Aboriginal Status – (% Yes)	1.8
Some Food Insecurity – (% Yes)	15.5
Social Assistance – (% Yes)	7.5
Rural Geographic Location – (% Rural)	19.3
Insulin Use – (% Yes)	15.5
Sources of Heterogeneity	
Current Smoking Status – (% Current Smoker)	19.0
Heavy Drinkers – (% Yes)	6.9
BMI > 30.0 – (% Yes)	36.4
Physical Activity Index	
Active	14.5
Moderately Active	20.9
Inactive	64.6
Life Stress - %	
Not at all stressful	21.1
Not very stressful/a bit stressful	55.9
Quite a bit/extremely stressful	23.0
Family Member Smokes Inside House – (% Yes)	24.5
Marital Status – (% Married)	67.7
Sense of Belonging to the Community - %	
Strong	22.5
Somewhat strong	38.1
Somewhat weak	24.1
Weak	15.3
Regular Medical Doctor – (% Yes)	96.0
Self-Perceived Unmet Healthcare Needs	12.7
Health Utilities Index Mark 3 – Mean (SD)	0.78 (0.26)

[A] Number of medical conditions other than stroke, heart disease, osteoarthritis or depression

Table 5-4: Bivariate Associations between Determinants of Health and HRQL (N=4678)

	b	95% CI Lower Limit	95% CI Upper Limit	R	R$^2_{adj}$
Stage of Life Cycle					
Age^A				0.14	0.02
Age	**-0.003***	-0.004	-0.002		
Age^2	**-0.0001***	-0.0001	-0.00004		
Osteoarthritis	**-0.13***	-0.16	-0.10	0.20	0.04
Stroke	**-0.21***	-0.27	-0.15	0.17	0.03
Heart Disease	**-0.14***	-0.17	-0.11	0.21	0.05
Depression	**-0.22***	-0.27	-0.17	0.21	0.05
Number of Medical Conditions^B	**-0.07***	-0.07	-0.06	0.43	0.19
Duration of Diabetes^C				0.17	0.03
Less than 2.0 years	**0.10***	0.06	0.13		
2.0 years to 6.0 years	**0.12***	0.09	0.15		
6.0 years to 13.0 years	**0.07***	0.04	0.10		
13.0 years or longer	-	-	-		
Subpopulation Partitions					
Level of Education^D				0.15	0.02
Less than secondary	**-0.11***	-0.14	-0.07		
Secondary graduation	**-0.05***	-0.09	-0.01		
Some post-secondary, college, trade school	**-0.04***	-0.08	-0.01		
University degree	-	-	-		
Food Insecurity	**-0.18***	-0.21	-0.15	0.25	0.06
Social Assistance	**-0.21***	-0.26	-0.16	0.21	0.04
Aboriginal Status	-0.05	-0.12	0.02	0.03	0.01
Rural Geographic Location	0.004	-0.02	0.03	0.01	0.00
Male	**0.06***	0.03	0.08	0.11	0.01
Insulin Use	**-0.10***	-0.13	-0.06	0.13	0.02
Sources of Heterogeneity					
Current Smoker	**-0.05***	-0.08	-0.02	0.08	0.01
Heavy Drinker	**0.03***	-0.01	0.07	0.03	0.0
BMI > 30.0	**-0.06***	-0.08	-0.04	0.11	0.01
Physical Activity Index^E				0.20	0.04
Active	**0.11***	0.08	0.14		
Moderately Active	**0.11***	0.09	0.13		
Inactive	-	-	-		
Life Stress^F				0.22	0.05
Not at all stressful	-	-	-		
Not very stressful/a bit stressful	**-0.02***	-0.05	-0.0006		
Quite a bit/extremely stressful	**-0.15***	-0.19	-0.12		
Family Member Smokes Inside House	**-0.05***	-0.08	-0.02	0.08	0.01
Married	**0.08***	0.05	0.10	-0.13	0.02
Sense of Belonging to the Community^G				0.19	0.04
Strong	**0.14***	0.10	0.19		
Somewhat strong	**0.14***	0.10	0.18		
Somewhat weak	**0.09***	0.05	0.13		
Weak	-	-	-		
Regular Medical Doctor	-0.04	-0.09	0.01	0.03	0.00
Self-Perceived Unmet Healthcare Needs	**-0.18***	-0.22	-0.15	0.23	0.05

*$p<0.05$ (Significance based on bootstrap variance estimate); A Age was operationalized as a mean centered quadratic (b_1(age-61.55) + b_2(age-61.55)^2); thus, bivariate analysis included both (age-61.55) + b_2(age-61.55)^2; B Number of medical conditions other than stroke, heart disease, osteoarthritis or depression; C The bivariate analysis for duration of diabetes included three dummy variables to represent the first three quartiles of duration; the fourth quartile of duration was the reference category (i.e. greater than 13.0 years).; D The bivariate analysis for education included three dummy variables for the lower levels of education; college or university degree was the reference category.; E The bivariate analysis for physical activity included two dummy variables to represent active and moderately active; inactive was the reference category.; F In the bivariate analysis for life stress, dummy variables were used to represent not very stressful/a bit stressful and quite a bit/extremely stressful; not at all stressful was the reference category.; G The bivariate analysis for sense of belonging to the community included three dummy variables to represent strong, somewhat strong, and somewhat weak; weak was the reference category.

Table 5-5: Unstandardized Regression Coefficients for Each Domain Alone and Overall Model (N=4678)

	Model 1 (Stage of Life Cycle)	Model 2 (Subpopulation Partitions)	Model 3 (Sources of Heterogeneity)	Model 4 (Overall model)
Stage of Life Cycle				
Age[A]				
Age	-0.001*			-0.003*
Age^{2}	-0.0001*			-0.0001*
Osteoarthritis	-0.08*			-0.06*
Stroke	-0.14*			-0.11*
Heart Disease	-0.07*			-0.05*
Depression	-0.16*			-0.11*
Number of Medical Conditions[B]	-0.05*			-0.04*
Duration of Diabetes[C]				
Less than 2.0 years	0.05*			0.03*
2.0 years to 6.0 years	0.07*			0.04*
6.0 years to 13.0 years	0.02*			0.01
13.0 years or longer	-			-
Subpopulation Partitions				
Level of Education[D]				
Less than secondary		-0.09*		-0.04*
Secondary graduation		-0.03		-0.03
Some post-secondary, college, trade school		-0.04*		-0.02
University degree		-		-
Food Insecurity		-0.13*		-0.08*
Social Assistance		-0.12*		-0.07*
Aboriginal Status		0.02		-0.01
Rural Geographic Location		0.00		0.00
Male		0.03*		-0.01
Insulin Use		-0.08*		-0.04*
Sources of Heterogeneity				
Current Smoker			-0.01	-0.02
Heavy Drinker			0.04*	-0.01
BMI > 30.0			-0.04*	-0.03*
Physical Activity Index[E]				
Active			0.08*	0.06*
Moderately Active			0.09*	0.06*
Inactive			-	-
Life Stress[F]				
Not at all stressful			-	-
Not very stressful/a bit stressful			-0.02	-0.02
Quite a bit/extremely stressful			-0.11*	-0.08*
Family Member Smokes Inside House			-0.01	0.01
Married			0.06*	0.00
Sense of Belonging to the Community[G]				
Strong			0.11*	0.09*
Somewhat strong			0.11*	0.08*
Somewhat weak			0.07*	0.05*
Weak			-	-
Regular Medical Doctor			-0.06*	-0.01
Self-Perceived Unmet Healthcare Needs			-0.14*	-0.08*
	R=0.52	R=0.33	R=0.40	R=0.60
Variance Explained by Domain Alone	R^2_{adj}=0.27	R^2_{adj}=0.11	R^2_{adj}=0.16	R^2_{adj}=0.36
Unique Variance Explained by Domain[H]	R^2=0.15	R^2=0.02	R^2=0.06	

* $p<0.05$ (Significance based on bootstrap variance estimate); A Age was operationalized as a mean centered quadratic (b_1(age-61.55) + b_2(age-61.55)^2); B Number of medical conditions other than stroke, heart disease, osteoarthritis or depression; C Duration of diabetes > 13 years was the reference category; D College or university degree was the reference category. E Inactive was the reference category; F Not at all stressful was the reference category; G Weak was the reference category; H For example, R^2 change when Stage of Life Cycle variables are added to a model containing Subpopulation Partitions and Sources of Heterogeneity

Figure 5-1: Relationship between Stage of Life Cycle, Subpopulation Partitions, Sources of Heterogeneity

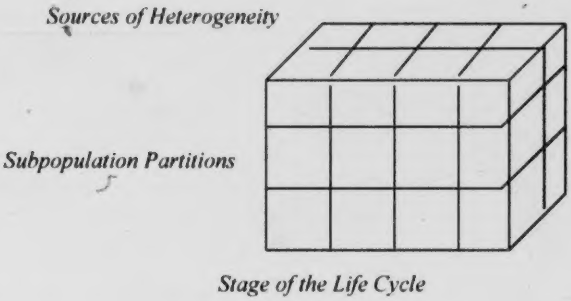


Figure 5-2: Algorithm for Differentiating between Individuals with Type 1 and Type 2 Diabetes

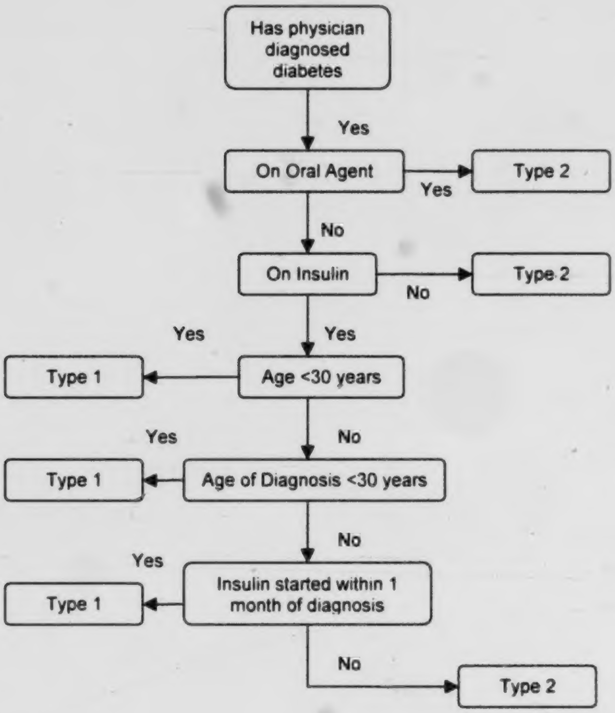
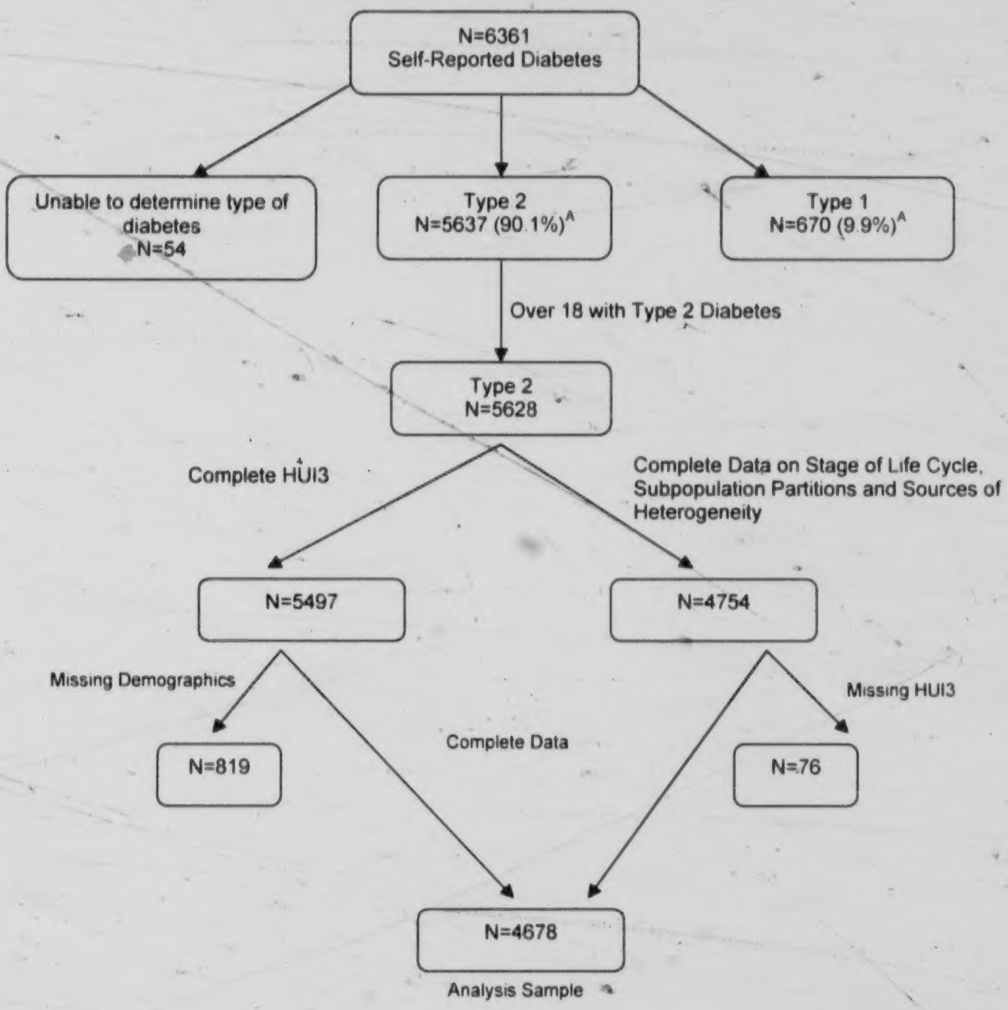

Has physician diagnosed diabetes
Yes
On Oral Agent
Yes
Type 2
No
On Insulin
No
Type 2
Yes
Yes
Type 1
Age <30 years
Yes
No
Type 1
Age of Diagnosis <30 years
No
Yes
Type 1
Insulin started within 1 month of diagnosis
No
Type 2

Figure 5-3: Survey Sample, Analysis Sample and Missing Data



A Percentage represents the weighted population percentage based upon respondents who could be categorized as having type 1 or type 2 diabetes.

Figure 5-4a: Nonlinear Bivariate Association between Age and HRQL Prior to Mean Centering

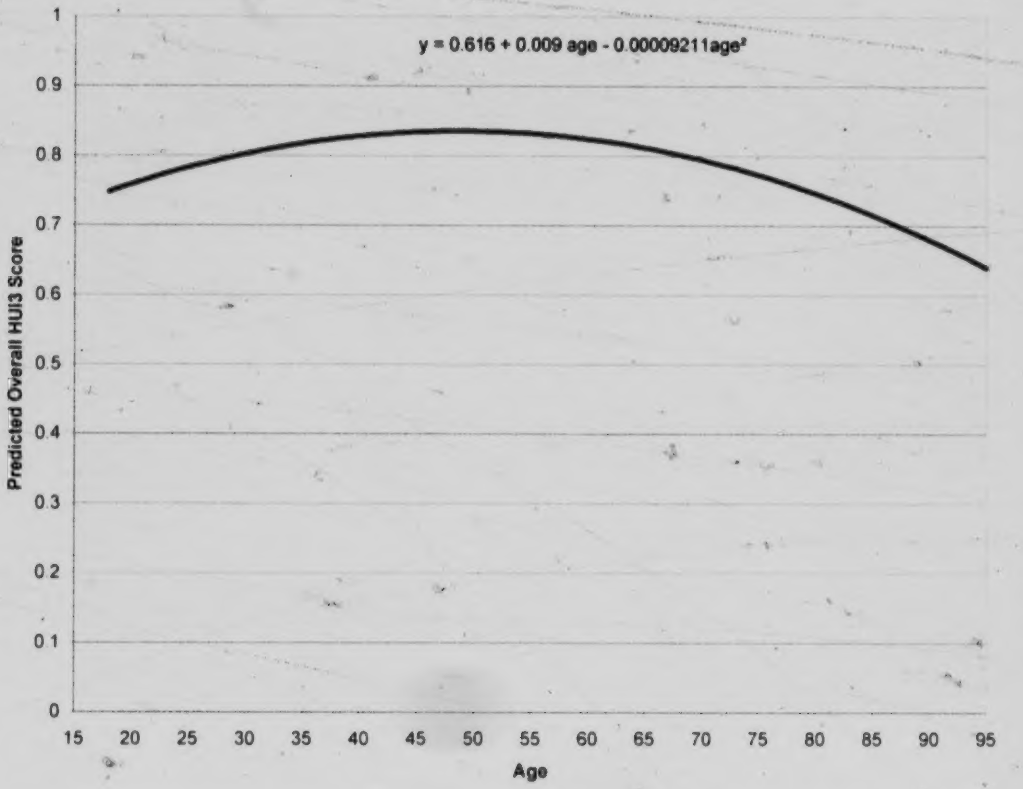
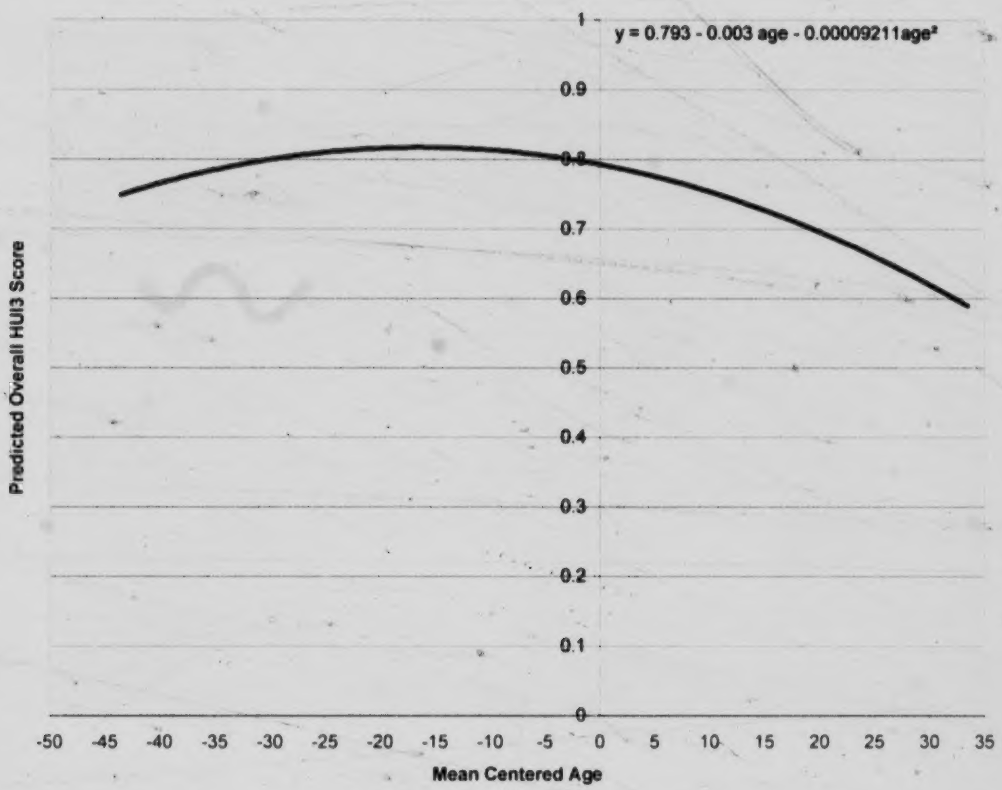
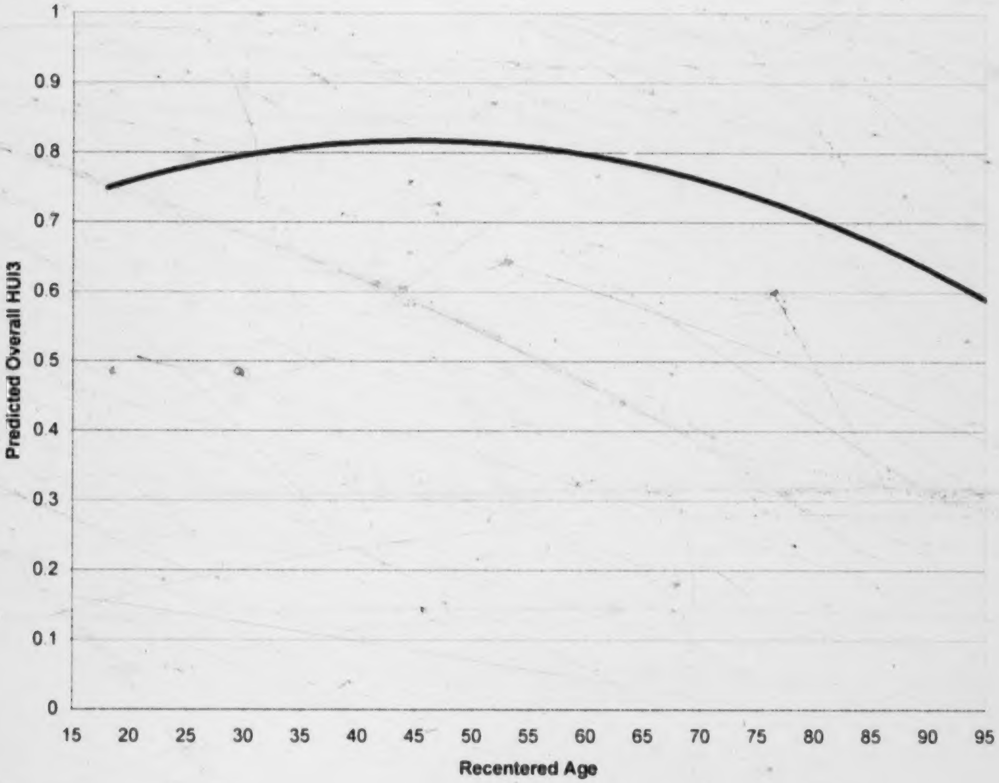


Figure 5-4b: Nonlinear Bivariate Association between Mean Centered Age^A and HRQL



A Mean Centered Age = Age minus 61.55

Figure 5-4c: Bivariate Association between Age and Predicted Overall HUI3 Scores from Mean Centered Quadratic



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Chapter 6 – Summary

6.1.0 Introduction

Health-related quality of life (HRQL) is an important outcome in chronic diseases such as diabetes, particularly from a patient perspective. In order for HRQL data to be useful in informing policy or clinical decisions, it is essential that these data are measured using an instrument that is valid in the particular disease being considered. Determining the degree to which a HRQL measure has construct validity in a certain disease or specific population requires the accumulation of evidence. Because generic measures of HRQL can be used in multiple diseases, they permit comparisons to be made across diseases and are useful in population health applications. As well, in type 2 diabetes in particular, generic measures of HRQL can potentially provide useful information about the additional burden related to comorbidities. Diabetes specific measures are, by definition and design, limited in this capacity. At the same time, there must be evidence that the dimensions of HRQL that comprise generic measures are not so general that they fail to capture the burden associated with type 2 diabetes.

The goals of this program of research were twofold. The first was to assess the construct validity of three generic measures of HRQL in type 2 diabetes (the RAND-12, HUI2 and HUI3). After having done so, the next goal was to evaluate a broad range of determinants of health in type 2 diabetes, using the HUI3 to measure HRQL. As construct validity requires the accumulation of evidence, multiple approaches to construct validity were used (known groups comparisons, interscale correlations, and associations between

HRQL and health care resource utilization) and analyses were performed in different samples (specifically for the HUI3) of people with type 2 diabetes.

6.2.0 Construct Validity of Generic HRQL Measures

The first objective was successful in that evidence was generated to support the use of all three generic HRQL measures in type 2 diabetes. Physical health and mental health are two broad health domains that are affected by diabetes and its complications, so, as expected, the RAND-12 performed reasonably well in discriminating between individuals who differed according to duration of diabetes, insulin use and days off work for diabetes. The HUI2 and HUI3 contain multiple attributes (i.e. emotion, pain, ambulation, etc.) likely to be affected by diabetes and its comorbidities or complications. For this reason it was expected that the HUI2 and HUI3 would also have cross-sectional construct validity in type 2 diabetes. The HUI2 and HUI3 overall scores did discriminate well between known groups (i.e. according to duration of diabetes, treatment regimen, days off work, emergency room visits, and comorbidities), with larger differences detected by the HUI3. This was one reason that the HUI3 would likely be preferred in type 2 diabetes over the HUI2. Evidence of the ability of the HUI3 to discriminate according to duration of diabetes and treatment regimen was generated in multiple study samples (i.e. in rural Albertans and in the general Canadian population), which increased our confidence in the performance of the HUI3 in type 2 diabetes.

Known groups comparisons were not the only source of evidence of construct validity of the three measures. The moderate to strong interscale correlations between the physical and mental health composites of the RAND-12 and attributes of the HUI2 and HUI3 that reflected similar dimensions (i.e. emotion, pain, and ambulation) were an additional source of construct validity. For the HUI3, the association between its overall scores and healthcare resource utilization provided further evidence of construct validity. Poor HRQL was associated with increased likelihood of emergency room visits, hospitalizations, and being above the median number of physician visits.

A literature review did not produce any published studies that assessed the construct validity of the RAND-12, HUI2 or HUI3 in type 2 diabetes. Very few, if any studies, have even measured HRQL with these instruments in diabetes. One study assessed HRQL using the HUI3 in diabetes and demonstrated that the illness burden of diabetes was largely associated with comorbid medical conditions (i.e. heart disease, stroke and arthritis), rather than the disease itself.(1) The findings of this previous analysis of disease burden in diabetes are consistent with the population-based analyses of Chapter 4 where the HUI3 discriminated well between respondents with and without heart disease or stroke.

The RAND-36 has been used to assess HRQL in diabetes in past research. Similar to the RAND-12, physical and mental health composite scores can be obtained with this measure. Macrovascular complications have been associated with large deficits on the RAND-36 physical and mental health composites in type 1 diabetes(2) and heart disease has been associated with physical health deficits in type 2 diabetes.(3) In type 2 diabetes, a relationship between duration of diabetes and physical health scores was demonstrated with the RAND-36. While the RAND-36 and RAND-12 both produce physical and mental health composite scores, there is potential for loss of information using the RAND-12 compared to the RAND-36. Thus, it was not clear if the RAND-12 would discriminate as the RAND-36 did in previous research. Differences between type 1 and type 2 diabetes also brought into question the generalizability of previous research using the RAND-36. The current findings for the RAND-12 in type 2 diabetes were, however, similar to those previously observed with the RAND-36, despite these differences.

6.2.1 Relevance - Construct Validity Evidence

The first three studies in this dissertation provided evidence to support the use of a generic health profile (the RAND-12) or two preference-based index measures (the HUI2 and HUI3) in type 2 diabetes in two different contexts: a controlled trial and a population health survey. This research is the first work applying the RAND-12, HUI2, and HUI3 to HRQL measurement in type 2 diabetes; thus, it has relevance to potential users of the instruments themselves and users of data generated from them, including clinicians, researchers and policy makers.

For clinicians, HRQL or health status information provided by any of the three instruments could complement clinical information, and this may help obtain a more complete understanding of the disease and treatment burden experienced by a patient. Looking at health status on separate domains using the RAND-12 or single attributes of the HUI or HUI3 is important as treatment may affect multiple domains of health differentially. Insulin use, for example, can improve glycemic control in type 2 diabetes, but can be associated with HRQL deficits due to perceived treatment burden.(4-6) Further, valid information on physical and mental health status provided from the RAND-12 or HUI3 could alert a clinician to unmet healthcare needs in a specific area. For instance, an individual's physical health needs could be well addressed, but at the same time problems with mental health or emotion may require attention. Thus, the RAND-12 or HUI single attributes may be useful in type 2 diabetes as a tool for detecting differential disease burden or treatment effects in a particular patient. The evidence of construct validity of the overall HUI3 score demonstrated that index scores could potentially be useful for determining the 'net' disease burden in type 2 diabetes. This could increase clinicians' level of confidence in decisions supplemented with HUI3 data in patients with type 2 diabetes, as it appeared that the overall score did in fact capture burden that is important in the disease.

The evidence of construct validity of the RAND-12, HUI2 and HUI3 generated by this program of research has relevance to researchers who wish to study HRQL in type 2 diabetes using these measures. Evidence that both dimensions of the RAND-12 discriminated according to disease severity provides the rationale for using the RAND-12 to measure health status in future cross-sectional studies in type 2 diabetes. Such applications might include comparing the physical and mental health burden of different diseases or comparing the burden of different segments of the population with type 2 diabetes (e.g. Aboriginals versus non-Aboriginals or individuals of different socio-economic status). This initial evidence of construct validity of the RAND-12 in type 2 diabetes does not only provide supporting evidence for choosing the RAND-12, but it could also increase researchers' confidence in inferences made from cross-sectional study results where health status was assessed using this instrument.

For researchers, evidence of the construct validity of the HUI2 and HUI3 in type 2 diabetes also has important implications. Similar to the RAND-12, it was important to provide some initial evidence that these measures do discriminate so that they could be used in cross-sectional applications. Further, exploring differences between the HUI2 and HUI3 was of key importance as it was clear that the two measures produced different utility scores. Knowing that the HUI3 utilities better estimate the burden associated with type 2 diabetes (i.e. that the HUI2 may underestimate the true burden) is critical as the utilities generated from either instrument can be used in various applications and would produce different results. The utilities generated from the HUI2 and HUI3 could be used in cost-utility analyses or in health adjusted life expectancy applications.

Population level evidence of construct validity of the HUI3 in type 2 diabetes has unique importance. As the HUI3 is used to measure HRQL in a number of Statistics Canada's surveys (the Canadian Community Health Survey, National Population Health Survey, the General Social Survey, etc.), it is important to generate evidence of construct validity of the HUI3 in various diseases. With such evidence researchers can then be confident in the inferences they make about particular diseases at the population level. Based on these analyses, it would be reasonable to use HUI3 utilities from population health surveys in utility based applications in type 2 diabetes. Such data may be useful, for example, in the expansion of the National Diabetes Surveillance System (NDSS)(7), which has initially focussed on epidemiologic trends of the incidence, prevalence and mortality associated with diabetes using administrative data from provincial healthcare systems.

In order to base resource allocation decisions upon health status, it is important that the information used in these decisions is generated from measures that have evidence of validity in the populations or disease states under consideration. It may be useful to generate information about the magnitude of burden in type 2 diabetes using the RAND-12 and compare this information to other conditions. However, the lack of a single summary score, the disaggregated physical and mental health scores may make the interpretation of the scores difficult. In some situations, decision makers may not be able to determine where the greatest burden exists, for example if individuals with arthritis had higher physical health burden with little mental health burden, but individuals with diabetes had both physical and mental health burdens. However, the RAND-12 may provide important information on burden in a general sense, such as in the area of mental health in diabetes. As well, policy makers could use information about the level of burden in specific subgroups with diabetes to target the identification of effective interventions (e.g. those with low income or Aboriginals). They could be confident that the data was generated from an instrument that has some evidence of validity in type 2 diabetes. Thus, evidence of construct validity of the RAND-12 in type 2 diabetes remains important from a health policy perspective.

Cost-utility analysis has relevance at the policy level and this research demonstrated that the HUI3 is an appropriate source of utilities in type 2 diabetes for such analyses. Further, the overall index score generated from the HUI3 may be more consistent with the needs of decision makers, compared to scores provided by health profiles. Because this research provided evidence that disease burden and comorbidity burden was captured by the HUI3 at the population level, it can help to increase the confidence in decisions made about type 2 diabetes based on HRQL data from Statistics Canada's surveys.

In addition to generating evidence of construct validity, the first three studies will be were useful in demonstrating which domains and attributes of HRQL were affected by type 2 diabetes. It was apparent individuals with more severe or advanced diabetes or those with comorbidities experienced both physical and mental health burden. Those with more severe or advanced disease had greater deficits on the emotion, pain, and ambulation attributes of the HUI3. Deficits on these attributes were found in rural Albertans and in the Canadian community dwelling population with type 2 diabetes. The RAND-12 provided corroborating evidence in rural Albertans in that individuals presumed to have more severe or advanced disease had both physical and mental health deficits measured with this instrument as well.

Undoubtedly it is important to clinicians, researchers and policy makers to understand the dimensions of HRQL that are affected by type 2 diabetes, its treatment, and comorbidities. For clinicians, it is clearly important that the emotional problems need to be screened for and addressed. As well, it would appear that pain was a source of the physical health burden, so this is another area of concern for clinicians. For researchers, it is apparent that when choosing a HRQL measure in diabetes, it is important to select a measure that broadly includes physical and mental domains that reflect pain, mobility or ambulation and emotion. From a policy perspective, programs aimed at improving well-being or HRQL in diabetes need to focus on both physical and mental health.

6.2.2 Future Research - Construct Validity

While this research generated evidence of cross-sectional construct validity of the RAND-12, HUI2 and HUI3 in type 2 diabetes, there remains a need to explore the longitudinal construct validity of these measures in the disease. To our knowledge, the HUI3 has been used to assess HRQL in diabetes longitudinally in just one study.(8) Although this was not a formal assessment of the HUI3's ability to detect change in HRQL overtime in type 2 diabetes, the fact that a clinically important change was detected would suggest that the HUI3 is potentially useful for this purpose.

As it is likely that the RAND-12, HUI2 and HUI3 will be used in the future for evaluative purposes in type 2 diabetes (i.e. measuring change in intervention studies or within person change over time in health status), there is a need to assess their responsiveness to change. The HUI3 may have discriminated better than the HUI2, but this does not necessarily mean that it would be more responsive. It would be useful then to compare the responsiveness of these three measures (i.e., the RAND-12, HUI2 and HUI3) within a single study that perhaps included disease specific measures as a benchmark. Longitudinal construct validity should also be assessed by exploring correlation with change with other measures of change, such as disease specific measures. Ability to discriminate relative to a disease specific measure may also be important to determine.

Reliability is also an important psychometric property of a HRQL measure. The test-retest reliability of the RAND-12, HUI2 and HUI3 in type 2 diabetes should be assessed, for future follow-up studies. Assessing test-retest reliability was not possible in these cross-sectional analyses. Further, the inter-rater reliability of these measures in type 2 diabetes and at the population level should be assessed in future studies where proxy respondents are used.

6.3.0 Determinants of Health in Type 2 Diabetes

A broad range of determinants of health in type 2 diabetes were assessed using the HUI3 as a measure of HRQL in Chapter 5. The determinants of health analysis demonstrated that disease-related factors, social determinants of health, and health-related behaviours were all associated with clinically important HRQL deficits in type 2 diabetes. Many of these factors extend beyond the scope of the traditional medical focus on disease.

Comorbidities were important determinants of health in type 2 diabetes. Stroke and depression were associated with the largest deficits. However, the burden associated with osteoarthritis and heart disease was also clinically important. Diabetes related factors (i.e. insulin use and duration of diabetes) were determinants of health specific to this population. It is important to note that two markers of low socioeconomic status were associated with HRQL deficits more than twice the clinically important difference. Behavioural factors such as physical activity and stress were important, as well as sense of community belonging. Perceived difficulties with access to healthcare were associated with large HRQL deficits. Overall, it was apparent that the determinants of health in type 2 diabetes were broad and consistent with the conceptual framework that was used to select the variables for the analysis.

Previous research has explored determinants of health in type 2 diabetes, but generally studies do not use comprehensive determinants of health frameworks that include social, behavioural and disease-related determinants of health.(4;6;9-20) Thus, there is potential for past observed relationships to be confounded by other determinants. For the most part, however, employing Hertzman et al.'s conceptual scheme in this analysis demonstrated findings consistent with previous literature for those variables that had been previously assessed. We observed that comorbidities and socioeconomic status were important determinants within the conceptual scheme, even after controlling for other determinants of health, which was consistent with previous observations. Employing the full conceptual scheme did suggest, however, that some past relationships between determinants of health and HRQL in diabetes may have, indeed, been confounded by other determinants. Marital status and sex, for example, were not associated with HRQL after controlling for other determinants of health such as socioeconomic status, sense of belonging, and individual lifestyle factors (such as stress). As well, in this analysis, being Aboriginal was not an independent determinant of health after controlling for socioeconomic variables and comorbidities. This perhaps suggests that being Aboriginal in itself does not determine the health of individual with type 2 diabetes, but perhaps it is the health and social issues of this population that are more problematic.

To our knowledge, several variables, such as sense of belonging and self-perceived unmet healthcare needs, have not been previously explored as determinants of health in type 2 diabetes. Consistent with previous research in the general population, weak sense of belonging was associated with poor health.(21) The clinically important HRQL deficit associated with self-perceived unmet healthcare needs deserves attention. It is interesting that a review of the literature produced many studies that quantify unmet health care needs but very few that assessed the relationship between unmet healthcare needs and outcomes. One previous study was identified in which unmet health care needs were associated with subsequent mortality in the elderly.(22) This again emphasizes the importance of recognizing and treating health problems viewed by the patient as not being addressed, perhaps through innovative ways of improving or expediting access.

6.3.1 Relevance - Determinants of Health in Type 2 Diabetes

The factors that determine health in type 2 diabetes are important to clinicians, researchers and policy makers. The clinically important deficits associated with comorbidities demonstrate that prevention (when possible) and management of comorbidities could be vital to preserving or improving HRQL in type 2 diabetes. From a clinical perspective and broader health policy perspective, efforts at primary and secondary prevention of heart disease and stroke could have a significant impact on HRQL. Similarly, as depression is a comorbidity that carried a particularly large burden, perhaps better efforts are needed in screening and treatment of depression in diabetes. Pain control and weight management in osteoarthritis could potentially improve HRQL in type 2 diabetes.

The association between social indicators (such as education, food insecurity and social assistance) and HRQL in type 2 diabetes is likely most relevant to health policy. The clinically important HRQL deficits associated with low socioeconomic status persisted after adjusting for comorbidities and a number of other determinants. Diabetes has been labelled a 'public health epidemic' and strategies have been developed to deal with this epidemic. Clearly these strategies must consider the segment of the population with diabetes that experiences a significant burden, i.e. those with low socioeconomic status.

Identifying determinants of health in the Canadian population with type 2 diabetes is important from a research perspective and can provide the basis for future research in this area. This analysis demonstrated that the conceptual scheme was useful for studying determinants of health in type 2 diabetes. Thus, it may serve as a useful framework for variable selection in future studies of determinants of health in type 2 diabetes. Further, knowing which variables influence HRQL in type 2 diabetes may be useful in nonrandomized study designs. Our results may provide some guidance as to which determinants of health should be included in data collection such that between groups comparisons can be adjusted for any differences in these determinants.

Another important application of this analysis is that it demonstrated the magnitude of HRQL deficits associated with determinants of health that would be considered either mutable or immutable in the majority of disease management interventions or interventions to enhance HRQL in type 2 diabetes. For example, these interventions are not likely to impact attained education level, socioeconomic status, or sense of belonging. Managing cardiovascular risk, depression, osteoarthritis, and stress are, however, areas that an intervention could target in people with type 2 diabetes. Finally, the determinants of health analysis identified some interesting relationships that are likely worthy of future research. For example, sense of belonging to the community was associated with HRQL, but it was not clear through what mechanism.

6.3.2 Future Research - Determinants of Health in Type 2 Diabetes

While our analysis confirmed and revealed some interesting relationship between HRQL and determinants of health in type 2 diabetes, future research in this area could further our understanding. One key limitation of this research was that it was cross-sectional; a longitudinal analysis of the determinants of health in type 2 diabetes would be beneficial. It would be useful, for example, to explore the impact of developing comorbidities. Changes in physical activity, BMI, and life stress and their relationship with HRQL would also be interesting to assess. Further, since endogeneity may have been an issue with some variables and, due to the fact that there were likely relationships between determinants of health, future analyses might employ a structural equation modelling approach to address these issues.

As this analysis did not contain information about treatment, future determinants of health models might include more clinical information about appropriateness of management and overall treatment burden. Ability to cope with the diabetes regimen (i.e. overall treatment satisfaction) may be important to include as well. Other aspects of the conceptual scheme could not be operationalized. Social capital could not be included in the true sense in that aggregate level indicators of community cohesiveness were not available. This variable may be a useful indicator of the social environment in future research. Other information on the physical environment may also be useful in future determinants of health models.

6.4.0 Summary

From this program of research it was apparent that the RAND-12 and HUI2 were acceptable choices for studying HRQL in type 2 diabetes. The HUI3, however, performed well in the condition and appeared to have advantages over the other measures. Evidence of the validity of preference-based measures such as the HUI3 in type 2 diabetes will be helpful in future analyses aiming to inform resource allocation decisions. This is particularly true of population-based applications; thus, it was important to provide evidence of the construct validity of the HUI3 at the population level. Based on the accumulation of evidence across two different samples, the HUI3 performed well in type 2 diabetes cross-sectionally. Future research is needed to assess the performance of the HUI3 in type 2 diabetes longitudinally. Using the HUI3 to explore the determinants of health in type 2 diabetes emphasized the contribution of clinical, social, behavioural and health care system factors to the overall health of individuals with this disease. The clinically important deficits associated with comorbidities emphasize the importance of primary prevention, secondary prevention and appropriate treatment and management. At the same time, it is evident that socioeconomic status also made a significant contribution to HRQL in type 2 diabetes and is an important, but likely more difficult factor, to address. The full determinants of health model suggest the overall health of people with type 2 diabetes is a societal concern, not just a concern of the health care system.

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Appendix A - The RAND-12

Physical Health Composite

1. In general, would you say your health is:

Response options:
1 = Excellent
2 = Very good
3 = Good
4 = Fair
5 = Poor

The following items are about activities you might do during a typical day. Does your **health now limit you** in these activities? If so, how much?

Response options:
1 = Yes, limited a lot
2 = Yes, limited a little
3 = No, not limited at all

2. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling or playing golf

3. Climbing **several** flights of stairs

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

Response options:
1 = Yes
2 = No

4. **Accomplished less** than you would like

5. Were limited in the **kind** of work or other activities

8. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

Response options:
1 = Not at all
2 = A little bit
3 = Moderately
4 = Quite a bit
5 = Extremely

Mental Health Composite

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

Response options: 1 = Yes
2 = No

6. **Accomplished less** than you would like

7. Didn't do work or other activities as **carefully** as usual

The following questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much time during the **past 4 weeks**:

Response options: 1 = All of the time
2 = Most of the time
3 = A good bit of the time
4 = Some of the time
5 = A little of the time
6 = None of the time

9. Have you felt calm and peaceful?

10. Did you have a lot of energy?

11. Have you felt downhearted or blue?

12. During the **past 4 weeks**, how much of the time has **your physical or emotional problems** interfered with your social activities (like visiting friends, relatives, etc.)?

Response options: 1 = All of the time
2 = Most of the time
3 = Some of the time
4 = A little of the time
5 = None of the time

Appendix B – The HUI2 Classification System

Attribute	Level	Utility[A]	Level Description
Sensation	1	1.0	Able to see, hear and speak normally for age
	2	0.87	Requires equipment to see or hear or speak
	3	0.65	Sees, hears or speaks with limitations even with equipment
	4	0.0	Blind, deaf or mute
Mobility	1	1.0	Able to walk, bend, lift, jump, and run normally for age
	2	0.92	Walks, bends, lifts, jumps, or runs with some limitations but does not require help
	3	0.61	Requires mechanical equipment (such as canes, crutches, braces or wheelchair) to walk or get around independently
	4	0.34	Requires the help of another person to walk or get around and requires mechanical equipment as well
	5	0.0	Unable to control or use arms and legs
Emotion	1	1.0	Generally happy and free from worry
	2	0.86	Occasionally fretful, irritable, anxious, depressed, or suffering night terrors
	3	0.60	Often fretful, irritable, anxious, depressed, or suffering night terrors
	4	0.37	Almost always fretful, irritable, anxious or depressed
	5	0.0	Extremely fretful, irritable, anxious or depressed usually requiring hospitalization or psychiatric institutional care
Cognition	1	1.0	Learns and remembers schoolwork normally for age
	2	0.85	Learns and remembers schoolwork more slowly than classmates as judged by parents and/or teachers
	3	0.55	Learns and remembers very slowly and usually requires special educational assistance
	4	0.00	Unable to learn and remember
Self-care	1	1.0	Eats, bathes, dresses, and uses the toilet normally for age
	2	0.85	Eats, bathes, dresses, or uses the toilet independently with difficulty
	3	0.55	Requires mechanical equipment to eat, bathe, dress or use the toilet independently
	4	0.00	Requires the help of another person to eat, bathe, dress or use the toilet
Pain	1	1.0	Free or pain and discomfort
	2	0.95	Occasional pain; discomfort relieved by nonprescription drugs or self-control activity without disruption of normal activities
	3	0.75	Frequent pain; discomfort relieved by oral medicines with occasional disruption of normal activities
	4	0.42	Frequent pain, frequent disruption of normal activities; discomfort requires prescription narcotics for relief
	5	0.00	Severe pain; pain not relieved by drugs and constantly disrupts normal activities

Source: http://www.fes.mcmaster.ca/hug/index.htm

A Single Attribute Utility Score

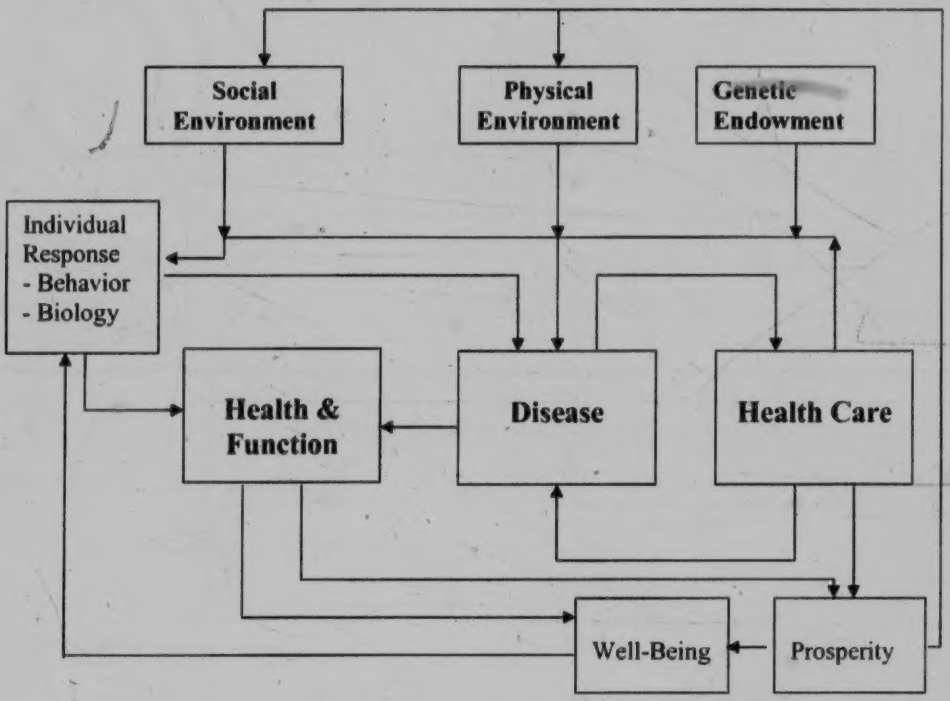
Appendix C - HUI3 Health Status Classification System

Attribute	Level	Utility[A]	Level Description
Vision	1	1.00	Able to see well enough to read ordinary newsprint and recognize a friend on the other side of the street, without glasses or contact lenses
	2	0.95	Able to see well enough to read ordinary newsprint and recognize a friend on the other side of the street, but with glasses
	3	0.73	Able to read ordinary newsprint with or without glasses but unable to recognize a friend on the other side of the street, even with glasses
	4	0.59	Able to recognize a friend on the other side of the street with or without glasses but unable to read ordinary newsprint even with glasses
	5	0.38	Unable to read ordinary newsprint and unable to recognize a friend on the other side of the street, even with glasses
	6	0.00	Unable to see at all
Hearing	1	1.00	Able to hear what is said in a group conversation with at least three other people, without a hearing aid
	2	0.86	Able to hear what is said in a conversation with one other person in a quiet room without a hearing aid, but requires a hearing aid to hear what is said in a group conversation with at least three other people
	3	0.71	Able to hear what is said in a conversation with one other person in a quiet room with a hearing aid and able to hear what is said in a group conversation with at least three other people with a hearing aid
	4	0.48	Able to hear what is said in a conversation with one other person in a quiet room without a hearing aid, but unable to hear what is said in a group conversation with at least three other people even with a hearing aid
	5	0.32	Able to hear what is said in a conversation with one other person in a quiet room with a hearing aid, but unable to hear what is said in a group conversation with at least three other people even with a hearing aid
	6	0.00	Unable to hear at all
Speech	1	1.00	Able to be understood completely when speaking with strangers or friends
	2	0.82	Able to be understood partially when speaking with strangers but able to be understood completely when speaking with people who know the respondent well
	3	0.67	Able to be understood partially when speaking with strangers or people who know the respondent well
	4	0.41	Unable to be understood when speaking with strangers but able to be understood partially by people who know the respondent well
	5	0.00	Unable to be understood when speaking to other people (or unable to speak at all)
Ambulation	1	1.00	Able to walk around the neighborhood without difficulty and without walking equipment
	2	0.83	Able to walk around the neighborhood with difficulty, but does not require walking equipment or the help of another person
	3	0.67	Able to walk around the neighborhood with walking equipment, but without the help of another person
	4	0.36	Able to walk only short distances with walking equipment and requires a wheelchair to get around the neighborhood
	5	0.16	Unable to walk alone, even with walking equipment; able to walk short distances with the help of another person, and requires a wheelchair to get around the neighborhood
	6	0.00	Cannot walk at all

Dexterity	1	1.00	Full use of two hands and ten fingers
	2	0.88	Limitations in the use of hands or fingers, but does not require special tools or help of another person
	3	0.73	Limitations in the use of hands or fingers, is independent with use of special tools (does not require the help of another person)
	4	0.45	Limitations in the use of hands or fingers, requires the help of another person for some tasks (not independent even with the use of special tools)
	5	0.20	Limitations in the use of hands or fingers, requires the help of another person for most tasks (not independent even with the use of special tools)
	6	0.00	Limitations in the use of hands or fingers, requires the help of another person for all tasks (not independent even with the use of special tools)
Emotion	1	1.00	Happy and interested in life
	2	0.91	Somewhat happy
	3	0.73	Somewhat unhappy
	4	0.33	Very unhappy
	5	0.00	So unhappy that life is not worthwhile
Cognition	1	1.00	Able to remember most things, think clearly and solve day to day problems
	2	0.86	Able to remember most things, but have a little difficulty when trying to think and solve day to day problems
	3	0.92	Somewhat forgetful, but able to think clearly and solve day to day problems
	4	0.70	Somewhat forgetful, and have a little difficulty when trying to think or solve day to day problems
	5	0.32	Very forgetful, and have great difficulty when trying to think and or solve day to day problems
	6	0.00	Unable to remember anything at all, and unable to think or solve day to day problems
Pain	1	1.00	Free of pain and discomfort
	2	0.92	Mild to moderate pain that prevents no activities
	3	0.77	Moderate pain that prevents a few activities
	4	0.48	Moderate to severe pain that prevents some activities
	5	0.00	Severe pain that prevents most activities

Source: http://www.fcs.mcmaster.ca/hug/index.htm
A Single Attribute Utility Score

Appendix D: CIAR Population Health Framework[5]



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[5] Evans RG, Stoddart GL. Producing health, consuming health care. Social Science and Medicine 1990; 31: 1347-63.